Case Based Pediatrics For Medical Students And Residents

Department of Pediatrics
University of Hawaii John A. Burns School of Medicine

Editors
Loren G. Yamamoto, MD, MPH, MBA
Alson S. Inaba, MD
Jeffrey K. Okamoto, MD
Mary Elaine Patrinos, MD
Vince K. Yamashiroya, MD

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Case Based Pediatrics For Medical Students and Residents - Contributors

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Chapter I.1. Pediatric Primary Care
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A six year old male presents to your office for his annual well child visit. He is accompanied by his mother. You have cared for this child since his birth, and he has had regular well child care. You last saw him for his visit prior to entering kindergarten at age five years. Today his mother notes that she has been anxiously awaiting this visit as she has several concerns to discuss:

1. He is having some difficulty in school (now just finishing the first quarter of first grade). He is struggling to learn to read, and has some difficulty with arithmetic. His teacher called his mother yesterday to report that he hasn't been turning in his homework or completing his classroom assignments. His mother indicates that she was very surprised to hear this, as the previous teacher reports have indicated that he was doing adequate work.
2. He has frequent complaints of stomachache. He has a good appetite, but has always been a "picky eater". He enjoys drinking milk.
3. He has been having increasing nasal congestion over the last few months. He has had some sneezing attacks, and seems to clear his throat often. He does cough at night. The cough often sounds "wet" to his mother. He also joins in to tell you that he has a hard time breathing during PE. He has no other regular physical activity, but his mother reports that he is always "busy doing something". His mother reminds you that he was born prematurely at 34 weeks, and had difficulty with wheezing as a younger child, but he has done well in the last year or two and hasn't needed any medications for wheezing.

Exam: VS are normal. Weight 30 kg (66#) (> 95%ile), height 117 cm (46") (50%). In general, he appears to be an overweight, friendly child who is cooperative and who appears to be his stated age. He is active in the exam room, exploring the contents of the drawers and cabinets. He interrupts his mother repeatedly during the interview. He appears to be mouth breathing with significant nasal congestion. His tonsils are large but not inflamed. His heart is regular without murmurs. His pulses are normal. His lungs have clear breath sounds, with transmitted upper airway rhonchi. There are no wheezes, but the I:E ratio is prolonged. His abdominal and neurologic screening exams are normal.

The approach taken by a pediatrician when confronted with this patient with multiple complex complaints will vary considerably depending on factors such as training, availability of appropriate pediatric subspecialists, and past successes (or failures) when managing similar issues. As an example, the patient presented above could be referred to a psychologist for an educational assessment, a psychiatrist to manage possible ADHD, a gastroenterologist to manage his abdominal pain, an allergist, a pulmonologist, and possibly an otolaryngologist to evaluate his respiratory complaints, and a nutritionist or dietitian or weight management program to manage his obesity. It would be a daunting task to coordinate and manage all of these specialists, and it is likely that the parents would be thoroughly confused about how to improve his situation if they did receive input from all of these experts. On the other hand, a thoughtful pediatrician could successfully manage all of these issues without any consultations at all. Most pediatricians would probably develop a plan of care somewhere between these two extremes, using selected specialists to assist in the area of concern that they feel least comfortable managing.

The medical home is a concept in which a primary care provider is the ultimate source of all health care for a child. This would include acute care visits for illnesses and injuries, anticipatory guidance, immunizations, growth and development monitoring, preventive health maintenance, and especially for children with special health care needs; the coordination of care among other medical and nonmedical specialists (audiology, speech therapy, child development programs, school programs, etc.).

Although acute care office visits for illnesses and injuries are an important part of what pediatricians do, a significant component of pediatric primary care consists of anticipatory guidance, immunizations, growth and development monitoring, and preventive health maintenance (1). Coordination of care and providing after hours care are areas where there is a large amount of variation in approach. This variation is partly a result of personal style and choices, but it is also significantly influenced by location and type of practice. For example, a solo rural pediatrician would not be able to limit his/her availability after hours for emergencies in the same way that a pediatrician employed by a large group that provides full after hours coverage for emergencies, newborns and telephone triage would be able to. Even in urban areas with lots of coverage for emergency care and newborns, pediatricians vary in their accessibility to their patients. Some parents are told not to call their pediatrician after hours "unless it is an emergency", while others work with pediatricians who provide their home phone number and are easily accessible through an answering service for after hours concerns. Those pediatricians find that while many families feel comforted by the knowledge that they could reach their doctor easily if they needed to, not many families abuse the privilege.

Another area of after hours care with great variability is the use of the emergency room to manage illness when the office is closed. Some pediatricians are not available to their patients for after hours advice at all, with their answering machine directing parents with concerns to take the patient to the nearest emergency room. Most pediatricians will discuss concerns that a parent may have after hours; the difficulty then is that you must offer advice about whether to seek care in the emergency room or wait until the office is again open. Concern about liability may cause some physicians to send most patients to the emergency room, particularly if there is another physician there who will see the child (so that they do not have to go in themselves). That will then transfer the problem to someone else, and an exam will be performed so that you are no longer accepting the parental observations as your only source of information. Unfortunately this is a very expensive way to provide care, so many pediatricians try to refer only those patients who sound like they might benefit from emergency care. Determining which patients should go becomes even more difficult when covering for a colleague after hours. Part of the decision making often includes knowledge of prior interactions with the parents. When the parents are strangers, it is more likely that they will be sent to the ER if they call with concerns.

As primary care physicians, pediatricians are the first to be consulted by many parents for a wide range of concerns. It is useful to have a basic management plan (or algorithm) for the most common complaints that come in, including an assessment of when referral to a specialist might make sense. In developing such an algorithm, a primary consideration will be the local availability of pediatric subspecialists. For example, it is not useful to decide that any child presenting with a heart murmur will be evaluated by a pediatric cardiologist, if the nearest available pediatric cardiologist is hundreds of miles away. The varying availability of subspecialty care is one of the factors involved in the observed variability in the medical care provided in one locale compared to another.

If a pediatric subspecialist is not available locally, the choices for a general pediatrician then become: a) evaluate and manage yourself, b) use a specialist who does not have pediatric subspecialty training, or c) send the patient to the specialist regardless of the

distance/expense/inconvenience involved. In some locations, you may also have the option of managing the patient using a specialist available to you by telemedicine, but this is not a widespread practice yet.

Certification is available from the American Board of Pediatrics in the following pediatric subspecialties: adolescent medicine, clinical and laboratory immunology, medical toxicology, pediatric cardiology, pediatric critical care medicine, pediatric emergency medicine, pediatric endocrinology, pediatric gastroenterology, pediatric hematology/oncology, pediatric infectious diseases, pediatric nephrology, neonatal-perinatal medicine, pediatric pulmonology, pediatric rheumatology, developmental-behavioral pediatrics, neurodevelopmental disabilities and sports medicine (2).

Subspecialty certification (from other specialty Boards) is also available in: pediatric otolaryngology, child and adolescent psychiatry, pediatric radiology, pediatric surgery, and pediatric pathology (3). Other specialties may offer additional pediatric training to their fellows to allow them to be designated as subspecialists. For example, pediatric orthopedists and pediatric ophthalmologists have additional training and skills necessary for the appropriate care of children.

Under traditional fee for service payment arrangements (doctors are paid for services that they deliver), access to pediatric subspecialty care was primarily limited by geographic availability. "Capitation" refers to a system in which physicians are paid a fixed amount per patient per month regardless of whether the patient is seen 20 times during the month or not at all. Capitation is risky in that physicians will not be adequately reimbursed for severe or chronically ill patients, but on average, this is offset by healthy patients who do not use the service. With other insurance payment arrangements covered under the umbrella of "managed care" (which may be pure capitation or a combination of capitation and fee for service), the access to pediatric subspecialty care may also be limited by the network of physicians who participate with (or are employed by) the health maintenance organization. A pediatrician who is deciding whether to contract with, or become employed by, a health maintenance organization may want to consider what degree of access to pediatric subspecialty care his/her patients will be able to count on. As access to subspecialists becomes more difficult, the primary care pediatrician will need to be able to provide more complex care for at least some of the patients in his/her panel.

The American Academy of Pediatrics has addressed these issues in several policy statements. For example, in "Guiding Principles for Managed Care Arrangements for the Health Care of Newborns, Infants, Children and Young Adults" (4), some major principles were outlined including:

1. Access to Appropriate Primary Care Pediatricians:

a. Choice of primary care clinicians for children must include pediatricians.

b. Primary care pediatricians (PCPs) should serve as the child's medical home and ensure the delivery of comprehensive preventive, acute, and chronic care services. They should be accessible 24 hours a day, 7 days a week, or have appropriate coverage arrangements.

c. The PCP should assume the role of the care coordinator (i.e., the physician who ensures that all referrals are medically necessary). The function of the PCP might be transferred to a pediatric medical subspecialist for certain children with complex physical and/or mental health problems (e.g., those with special health care needs, such as children with cystic fibrosis, juvenile rheumatoid arthritis) if the specialist assumes responsibility and financial risk for primary and specialty care. For certain physical, developmental, mental health, and social problems, the PCP may seek the assistance of a multidisciplinary team with participation by appropriate public programs (e.g., Title V Program for Children with Special Health Care Needs).

d. Families should receive education at the time of enrollment to help them understand fully how managed care arrangements work for their individual policies.

2. Access to Pediatric Specialty Services:

a. When children need the services of a physician specialist or other health care professionals, plans should use clinicians with appropriate pediatric training and expertise. Pediatric-trained physician specialists, including pediatric medical subspecialists and pediatric surgical specialists, should have completed an appropriate fellowship in their area of expertise and be certified by specialty boards in a timely fashion if certification is available. These physicians and other health care practitioners should be engaged actively in the ongoing practice of their pediatric specialty and should participate in continuing medical education in this area.

b. There should be no financial barriers to access for pediatric specialty care above and beyond customary plan requirements for specialty care.

c. Plans should contract with the appropriate number and mix of geographically accessible pediatric-trained physician specialists and tertiary care centers for children.

d. Referral criteria for pediatric specialty clinicians should be developed. These criteria may include age of the patient, specific diagnoses, severity of conditions, and logistic considerations (e.g., geographical access and cultural competence).

e. Processes for approving referrals to pediatric medical subspecialists and pediatric surgical specialists should be developed by health plans working collaboratively with PCPs and pediatric medical subspecialists and pediatric surgical specialists.

There is particular concern about pediatric specialty care for children with special health care needs. As stated in the AAP policy statement "Managed Care and Children with Special Health Care Needs: A Review" (5): Children with disabilities differ from adults with disabilities in a managed care environment in a variety of ways. Three major differences include the following: 1) The changing dynamics of child development affect the needs of these children at different developmental stages and alter their expected outcomes. Illness and disability can delay, sometimes irreversibly, a child's normal development. 2) The epidemiology and prevalence of childhood disabilities, with many rare or low incidence conditions and few common ones, differ markedly from that of adults, in which there are few rare conditions and several common ones. 3) Because of children's need for adult protection and guidance, their health and development depend greatly on their families' health and socioeconomic status.

This policy also states, "Children with disabilities and other chronic conditions that may lead to disability require the services of pediatric subspecialists in addition to primary care pediatricians. Access and availability of pediatric subspecialty services must not be significantly impeded by managed care arrangements. Although it is ideal for the primary care physician to manage and coordinate the care for a child's health needs, the complex or rare nature of a particular child's condition may make it difficult for the primary care physician to meet all of the needs of the child and family adequately without additional expertise" (5).

A good pediatric primary care physician should also work with non-physician partners. Interactions with school personnel, public health nurses, social workers, various therapists (such as speech/language therapists, occupational therapists, physical therapists), early

childhood educators or daycare providers are a common part of pediatric practice today. Learning to interact appropriately with these individuals, and to gain from their expertise, is an important part of pediatric training.

Primary care pediatrics can be very challenging. Although there is a perception that office based pediatrics is largely limited to runny noses and ear infections, in fact there is a wide realm of issues and problems that a pediatrician may become involved in. The nature of the practice will depend to some extent on the ease of availability of subspeciality care, but will also depend on personal characteristics of the pediatrician that determine the practice style he or she is most comfortable with.

Questions

1. True/False: When caring for pediatric patients, it is always more appropriate to use pediatric subspecialists than specialists who may be primarily trained to work with adults.

2. True/False: There is a standard for after hours accessibility that all pediatricians adhere to.

3. True/False: There is variability in the use of pediatric subspecialty care that results from factors other than availability of specialists.

4. If a pediatric subspecialist is not available, the pediatrician has the following choices:
   a. Evaluate and manage the patient without referral.
   b. Use a specialist who does not have pediatric subspecialty training.
   c. Send the patient to a pediatric subspecialist regardless of cost and inconvenience.
   d. All of the above.

5. Pediatricians may be concerned about giving after hours telephone advice to parents who call. This concern may be dealt with by:
   a. Refusing to talk with parents after hours.
   b. Referring all parents who call to take their child to the ER.
   c. Only giving advice to parents who are familiar and reliable.
   d. Ignoring concerns and giving advice to any parent who calls.
   e. All of the above may be considered appropriate.

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2. "Pediatric Subspecialties" http://www.abp.org/STATS/WRKFRC/SUBS.HTM
3. "ABMS Member Boards: Subspecialty Certificates Issued" http://www.abms.org/approved.asp
4. AAP Committee on Child Health Financing. Guiding Principles for Managed Care Arrangements for the Health Care of Newborns, Infants, Children, Adolescents, and Young Adults (RE9932). Pediatrics 2000;105(1):132-135.
5. AAP Committee on Children with Disabilities. Managed Care and Children With Special Health Care Needs: A Subject Review (RE9814). Pediatrics 1998;102(3):657-660.

Answers to questions

1. False. Proximity to the patient is also an important factor. A general surgeon practicing in a small town might be the best person to handle a suspected case of appendicitis, for example.
2. False. Although some third party payors have standards written into their contracts with physicians, and the American Academy of Pediatrics has created a standard, not all pediatricians adhere to these standards.
3. True. Many factors are involved, including the training of the primary care pediatrician and past experience with similar cases.
4. d
5. e

Chapter I.2. Growth Monitoring
Vince K. Yamashiroya, MD

A 4 month old Asian female comes to your office for her scheduled well baby checkup. She was born at 39-4/7 weeks gestation by normal spontaneous vaginal delivery without any complications. At birth, her weight was 3856 g, length 53 cm, head circumference 34 cm, and chest circumference 35.5 cm. She was discharged from the nursery at 48 hours of life. She has been breast-fed since birth, although her mother started to also use formula between one to two months of age. She is now being breast-fed once a day, given pumped breast milk in a bottle two to three times a day, and formula the rest of the time (about 16 oz or 480 ml per day). She has 2 to 3 bowel movements a day with many wet diapers. Her past medical history is otherwise significant for a vibratory heart murmur heard from the second week of life, which was thought to be innocent. Parents have no concerns.

Exam: VS are normal. Weight 7.4 kg (95%tile), length 64 cm (90%tile), head circumference 43 cm (90%tile), and chest circumference 41 cm. She is a robust, active and healthy appearing infant. Her heart murmur has resolved and the rest of her examination is otherwise normal.

The monitoring of a child's growth is probably the most important job for a pediatrician. It is not only essential for the general pediatrician, but for other subspecialties as well. An aberration in growth patterns is often the first clue that there is something wrong with the child. Often, the growth of the child is used in conjunction with other signs and symptoms, to help the physician determine what the problem might be. An older child who is not gaining weight could be the first clue to inflammatory bowel disease. A girl who is short in stature may have Turner syndrome. A baby with an abnormally increasing head size might have hydrocephalus.

The most important tool for assessing and monitoring a child's growth is the growth chart which plots height (length), weight and head circumference. There are different growth charts for boys and girls. There are two age group specific growth charts, one for children from birth to 36 months of age, and another from 2 years to 20 years of age.

The National Center For Health Statistics (HCHS) of the Centers for Disease Control and Prevention, recently released new standard growth charts in 2000 that remedy many of the deficiencies present in older growth charts. The new growth charts are based on a national representative sample collected from 1988 to 1994 as part of the National Health and Nutrition Examination Survey (NHANES-III), and they better represent the combined growth patterns of breast-fed and formula-fed infants. The larger, pooled data sets used to create the revised charts eliminate the problem of differing percentiles when making the transition from recumbent length to stature height. Lastly, the weight for height curves have been replaced by body mass index (BMI) curves. Other new features of the new growth charts are the extension to 20 years because of sufficient data being available and its desirability for general populations, particularly for clinics dealing with endocrine disorders and congenital abnormalities (1).

It should be noted that these growth charts are reflective of the population who are healthy and born at term. There are other growth charts available for children with various conditions, such as Turner, Klinefelter and Down syndromes and achondroplasia (2). Special growth charts for premature babies are also available by Babson and Benda that are based on gestational rather than chronological age, beginning at 26 weeks of gestation (3). Unfortunately, these charts are based on a relatively small, possibly non-representative sample (4). If the NCHS growth charts are used, however; the child's growth parameters (weight, height, head circumference) should be adjusted for prematurity until 24 months of age or up to three years for infants born at less than 1500 grams (5). Very low birth weight (VLBW < 1,500 g) infants may continue to show catch-up growth through early school age.

It is essential to look at the trajectory of the child's growth curve. Typically, infants and children stay within one or two growth percentile channels, which is due to the control that genes exert over body size. A growth channel is the area between the percentile lines. A normal exception occurs during the first two years of life. For full term infants, size at birth reflects the influence of the uterine environment. Size at age 2 years correlates with mean parental height, reflecting the influence of genes. Therefore, from birth through 18 months, small infants will often shift percentiles upward toward their parents' mean percentile, and large infants will shift downwards (4). A formula can be used to calculate the estimated adult height by taking the mid-parental height (mother's height + father's height, divided by 2), and adding 6.5 cm for males, and subtracting 6.5 cm for females, with a range of 2 standard deviations (one standard deviation is about 5 cm) (6). Growth is influenced by many factors, including nutrition, chronic disease, etc., therefore this formula is based purely on genetic potential.

In adolescents, normal variations in the timing of the growth spurt can lead to a misdiagnosis of growth abnormalities. In primary care, it is important to know the relationship between sexual maturity and growth, which is beyond the scope of this chapter. However, a few general rules can be kept in mind. Before the onset of puberty, the average height velocity is about 5 to 6 cm per year. In females, peak height velocity occurs about 2 years after the growth spurt begins and averages about 9 cm per year. This is also around the time when the nipple and areola have developed but before any other significant breast development (7), and about 6 to 12 months prior to menarche. After menarche, females will usually not grow more than 5 cm, with epiphyseal closure occurring about 2 years after. In males, peak height velocity occurs later and averages about 10 cm per year. This is about the time that the male's genitalia are fully developed. Males are taller because of this greater velocity of height in addition to having about 2 more years of prepubescent growth over females (8).

The growth curve is not linear but rather sigmoidal. Growth normally starts to slow down at about 12 to 15 months of age, which is reflected in the growth chart. The periods of rapid growth occur during the first 12 months of age, and from puberty until adulthood. The growth chart is an essential tool to diagnose failure to thrive (FTT) or growth failure. Although there are no universal criteria for FTT, most consider the diagnosis if the child's weight is below the 5th percentile or drops more than two major percentile lines. Calculation of weight gain in grams per day also allows more precise estimation of growth rate as can be seen in the table below. Neonates should gain weight at a rate of 15 g/kg/day (9).

Age	Approximate Daily Weight Gain	Approximate Monthly Weight Gain
0-3 mos	30 g	1 kg (2 lb)
3-6 mos	20 g	0.6 kg (1.25 lb)
6-9 mos	15 g	0.5 kg (1 lb)
9-12 mos	12 g	0.4 kg (12 oz)
1-3 yrs.	8 g	0.25 kg (8 oz)
4-6 yrs.	6 g	0.18 kg (6 oz)

Note: 30 g = 1 oz.

When curves are outside the 5th and 95th percentiles, it is useful to mention the age at which the growth parameter is at its median value (50th percentile). For example, if a 10 year old female weighs 18 kg, this weight is below the 5th percentile for a 10 year old; and, it is at the 50th percentile for a 5 year old. One could state that her weight age is 5 years, which is a better quantitative description of the growth abnormality.

The weight for height curves exceeding 120% of the median weight for height can also be an indicator for obesity. The problem with the weight for height curves is that they are applicable only from 2 years to 11.5 years for males and up to 10 years for females because of weight for height changes occurring with age after pubescence. The new growth charts remedy this by including the body mass index (BMI), which is weight in kilograms divided by the square of the height in meters. In adults, a BMI value greater than 25 units is widely accepted as being overweight and a value larger than 30 units is accepted as obesity. However, since the cutoff values for children differ with age and sex, they therefore must be based on percentiles, with the 85th percentile being suggested as the cutoff point for being overweight. This percentile is also justified by studies showing that the risk of large BMI values in adulthood and the prevalence of cardiovascular and other diseases increase dramatically for children ages 8 years and older who are over the 85th percentile for BMI. BMI values decrease from 2 years to 5 years of age, after which there is an increase to 20 years of age. The changes with age in BMI reference values reflect normal alterations in total body fat and fat-free mass. Fat-free mass increases with age in both sexes, but increases are more rapid in boys than in girls after age 13. Likewise, total body fat increases from 8 to 18 years in girls but decreases after age 14 in boys. Another interesting point is the time of rebound, or the point when the BMI values change from decreasing to increasing. It has been observed that individuals who rebound earlier than 5 years of age have higher BMI compared to those who rebound later after 5 years of age. This helps predict those individuals who are at risk for obesity later in childhood and adulthood. The disadvantage of using BMI is that it does not provide an accurate index of adiposity since it does not differentiate between lean tissue and bone from fat. However, BMI values correlate with total body fat, fat as a percentage of body weight (percent body fat), and the mass of all lean tissues (fat-free mass). Although percent body fat is the best measure of obesity, its measurement requires complex laboratory procedures. When BMI is used to identify obese children, there are many false negatives (obese children not identified) but few false positives (non-obese children classified as obese). Therefore, for the easy recognition of obese children, BMI is preferred over triceps skinfold thickness in girls, but triceps skinfold thickness may be more useful in boys (1).

Common student and board examination questions include the growth chart patterns for various diseases and conditions such as constitutional growth delay, familial short stature, nutritional insufficiency, and congenital pathologic short stature. The following list describes the characteristics of each (4).

1. Congenital pathologic short stature: These infants are born small and growth gradually tapers off throughout infancy. These babies are born with intrauterine growth retardation (IUGR), and are small for gestational age (SGA). Examples are chromosomal abnormalities, TORCH infections, teratogens, extreme prematurity, maternal smoking, etc.
2. Constitutional growth delay: In this type of delay, these patients enter puberty later; therefore, their growth spurt occurs later in adolescence. The growth curve has the following appearance: weight and height drop in their percentiles near the end of infancy, parallel the norm through middle childhood, and accelerate toward the end of adolescence. Adult size is normal or often taller than average because their duration of growth is longer than others. Frequently, one or both parents may have a history of short stature during childhood, delayed puberty, and eventual normal adult height. Delayed puberty can be identified by asking about age of menarche in mother and age at which father first started shaving. Tanner staging is also useful in evaluating these patients because of their delayed puberty.
3. Familial short stature: Infant and parents are small. Growth runs parallel to and just below the normal curves.
4. Nutritional insufficiency: In this condition, weight declines before length. Body mass index is also low.

Questions

1. What is the formula for calculating BMI?
2. At what age does the uterine environment play a role in the growth of a child versus the influence on growth by the genetic makeup?
3. What are two ways failure to thrive are recognized in a growth chart?
4. What percentile of BMI is considered the cutoff point for being overweight?
5. What is the approximate weight gain in grams per day for a healthy term infant from birth to 3 months of age?
6. At what age does rebound occur in BMI? If a child rebounds early, what is this predictive of?
7. What is a weakness of using BMI to identify obesity?
8. How do the growth curves for congenital pathologic short stature, constitutional growth delay, and familial short stature look like?
9. What is the formula used to estimate a child's adult height (Tanner's height prediction formula)?

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http://netxperience.org/medcalc, and MedMath by Dr. Phillip Cheng, which can be downloaded at http://www.pdacentral.at/palm/preview/45487.html.

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Answers to questions

1. BMI (kg/m2) = weight in kilograms divided by the square of the height in meters.
2. First 18 months of life.
3. a) If the child's weight is below the 5th percentile, or b) if weight drops more than two major percentile lines.
4. 85th percentile.
5. 30 grams, or 1 oz per day.
6. At 5 years of age. Those who rebound before 5 years have a higher risk of obesity in childhood and adulthood.
7. It does not provide an accurate index of adiposity since it does not differentiate between lean tissue and bone from fat.
8. Congenital pathologic short stature: infant born small and growth gradually tapers off throughout infancy. Constitutional growth delay: weight and height drop in their percentiles near the end of infancy, parallel the norm through middle childhood, and accelerate toward the end of adolescence. Adult size is normal. Familial short stature: Infant and parents are small. Growth runs parallel to and just below the normal curves.
9. Predicted adult height = (mother's height + father's height) divided by 2, and adding 6.5 cm for males, and subtracting 6.5 cm for females, with a range of 2 standard deviations (one standard deviation is about 5 cm).

Chapter I.3. Developmental Screening of Infants, Toddlers and Preschoolers

Jeffrey K. Okamoto, MD

Three 18 month old children with their respective families have been seen at the outpatient pediatrics clinic since birth. All three children superficially appear normal, growing well on their growth curves. The children have no dysmorphic features or other abnormal signs on physical exam. They have not had any serious illness or hospitalization. The physicians in the clinic are mandated to do a check of development but they do this somewhat differently from physician to physician. One physician uses a Denver II Developmental screen on selected visits. One physician uses a Parent Questionnaire (a particular one called the PEDS) routinely. Another physician asks questions to her parents but does not use any formal developmental screening instrument.

In actuality all three children have autism. All three families do not know their children have this.

The first child shows delays on the Denver II screen in the personal social area. With the Denver II, the parents are asked certain questions, and they relate he doesn't play pat-a-cake, indicate wants, wave bye-bye, imitate activities or help in the house at 18 months of age. On direct observation with the Denver II he doesn't play ball with the examiner. Also he is not saying any words including "mama" or "dada" at 18 months of age. In the gross and fine motor areas his development appears normal. He is referred to an early intervention program and is diagnosed with autism.

The mother of the second child answers "Yes" to three of the questions on the PEDS (Parents' Evaluation of Developmental Status) parent questionnaire: 1) Do you have any concerns about how your child understands what you say?, 2) Do you have any concerns about how your child behaves? and 3) Do you have any concerns about how your child gets along with others?. The mother answers "no" to the other questions on the questionnaire. On further questioning the child's family relates how she likes to play by herself, and is easy to care for as she doesn't need too much attention. They are worried that she doesn't talk as much as other children, with words being spoken but in ways that do not make sense. She is suspected to have autism, and is referred to a Developmental Behavioral Pediatrician who confirms the diagnosis after more elaborate evaluation. She is referred to an early intervention program.

The physician who asks questions directly to families, finds the parents of the third child slightly worried at the 18 month visit about the child not being cuddly and not seemingly not very attached to them. They are told to interact more at home with their toddler. Later at three years of age, the parents are very worried about the child's language but are told that many children are "late talkers". When the child is five years of age the school notes the child's aloofness, poor receptive and expressive language, and nonexistent social skills. The school psychologist evaluates the child and relates to the parents their child has autism. The parents become angry as they find that many characteristics they have seen in the past two to three years are noted by the school psychologist as signs of autism. They tell the psychologist that they feel that their physician should have figured this out earlier.

An important aspect of caring for children in a medical context is that they grow in multiple ways over time. There is an expectation that they will grow physically in size. They also develop cognitively, behaviorally, socially and motorically.

Unfortunately, there are a variety of medical conditions that are derangements in proper child development. These include common diagnoses such as mental retardation and language disorders. There are many more problems that are rare, such as most of the developmental disabilities with genetic etiologies. Other medical conditions, such as cancer, may impact child development because of the effects of chemotherapy on the brain, or because of child and parental stress. Developmental or behavioral conditions are thought to occur in 12 to 16% of children in the United States (1). Families expect physicians to identify developmental problems in their children and then help manage these concerns (2).

It is therefore particularly important for physicians to carefully and routinely evaluate children for problems in development and behavior. Physicians such as pediatricians and family practitioners have essential roles because of their frequent contact with children and their families. They have knowledge of normal and abnormal development unlike other professionals who are in touch with families.

Physicians commonly encounter children in well child visits, in the emergency room, and in the hospital. All of these contexts allow for some monitoring of a child's development, but the best time to do developmental screening is in a primary care context. In the emergency room or in the hospital, a child may show developmental regression. Directly observed developmental behavior may be different than when the child is well (3). Attention is focused on acute illness during ER and hospital conditions, which makes families less receptive to other aspects of child health and development. Families also have more trust with someone who gets to know their child and family well. They prefer hearing any bad news from their regularly seen provider (4).

Identifying children with cognitive, behavioral, social or motor problems can be difficult. Problems in development may be subtle. Glancing at a child in the clinic may not identify these problems. Obvious and severe problems are actually rare compared to more commonly seen but subtle problems. Also, children sometimes do not cooperate with assessments. Lastly, developmental expectations change with age. Risk factors change with time. A child that appears completely normal as an infant or toddler may not develop skills expected in the preschool or school age group periods.

But because a moderate percentage of children have developmental or behavioral problems, a physician requires solid strategies for determining if a child has an important lag or problem in development. The majority of children with developmental problems are not detected without standardized screening tests. Informal "eyeballing" of children and informal questioning of parents do not work well. There is a good chance of missing problems because of the need of looking at multiple domains in development. A physician asking about walking and other motor skills may miss language and other cognitive deficits. Research from Great Britain where clinical impression is used rather than screening tests is revealing. It has been found that only about half the children who need to be identified are found using physician clinical impression without a developmental screening instrument (5). Also, asking questions about developmental milestones without a screening tool finds less than 30% of children with developmental conditions (6).

Therefore several instruments have been developed to increase identifying children with problems. These tools should be used on whole populations of children as to not miss children with subtle (and sometimes not so subtle) problems. Children need to be identified early so that problems can be managed properly. Goals of early management include optimizing the child's development, and supporting families with these children well.

The Denver II is a very popular screening tool used in the United States and worldwide. It was developed by Dr. William Frankenburg at the University of Colorado Health Sciences Center in Denver. It is an example of a "hands on" screening tool that also allows for parental report for selected items. However, most of the items require direct observation of the child trying to do certain tasks. There are 125 tasks arranged in four domains: personal-social, fine motor-adaptive, language and gross motor. However, only a few items in each domain are required to screen a particular child at a selected age. It has several advantages including ease of administration, coverage of a good range of age groups to screen (from birth to about 6 years of age), and a normative sample that includes diversification of race, place of residence (urban, suburban, rural) and the mother's educational level (7). There are also very few screening tests that take less time (although clinicians still balk at the 20 minute administration time).

One type of screening that is growing in popularity, and bolstered by recent research findings is a standardized parent questionnaire. Parents' concerns about children are important. Some concerns, particularly with parental worries regarding speech-language, emotional, behavioral, fine motor and global problems were highly predictive of true problems (5). Concerns about the accuracy and bias of parent reporting, parent reading level, and their understanding of concepts regarding the standardized parent screening tools have not been shown to be major problems after research has been done regarding these tools. (6).

The PEDS (Parents' Evaluation of Developmental Status) is a recently developed and well researched example of a standardized parental questionnaire. Parents complete the 10 item questionnaire in the waiting room. It takes about two minutes for the clinician to interpret the questionnaire. The PEDS can guide the clinician in getting particular history from the parents and guide what elements to include on the exam. The interpretation also helps guide the clinician in whether to use a hands-on screening tool, give parental reassurance, monitor the child, or make specific referrals to other specialists (6).

There are common problems in using developmental screening tests. A very common problem is not administering the screen as it was intended. This is often done secondary to poor training in the screening tool or to save time. The Denver II takes about 20 minutes to administer and score (8). Parental questionnaires are often quicker as they can be given to the parents while they are in the waiting room, and then scored when they interact with the physician (7).

Another problem is to assume that the screening test done at one point in time will discover all children with every type of developmental problem (8). Because development is ongoing with time, and because measuring development at very young ages cannot evaluate the full complexity of the various developmental domains at later ages, it is important to continue to assess children using tools appropriate for their age throughout their entire development.

Fortunately the child attending school usually has such assessments administered by the school on a periodic basis. The job of the physician in developmental screening is especially important prior to the school years. Physicians can access early intervention services until 3 years of age and then special education programs from ages 3 to 5 years for their children with developmental concerns.

Questions

1. Developmental and behavioral conditions occur in approximately what percentage of children?
   a. 0.15%
   b. 1.5%
   c. 15%
   d. 50%
   e. 80%

2. What is the best clinical situation to try to identify children with developmental disorders from developmentally normal children?
   a. Primary care clinic
   b. Emergency room
   c. Hospital ward
   d. Pediatric intensive care unit
   e. All of the above are "best places"

3. Which of these following methods of identifying children with developmental or behavioral concerns has the worst sensitivity?
   a. "Hands on" developmental screening tool (such as the Denver II).
   b. Parent answered developmental questionnaire.
   c. Physician clinical impression about development, without a screening tool.
   d. Flagging all children in the Neonatal Intensive Care Unit (NICU) that have risk factors for disability.
   e. All have about equal sensitivity.

4. Which of the following have been proven problems regarding the standardized parent developmental screening tools?
   a. Concerns about the accuracy of parent reporting.
   b. Concerns about the bias of parent reporting.
   c. The tools are time consuming for the clinician to use.
   d. Understanding of concepts by parents.
   e. All of the above are not problems according to research.

5. Common problems in using developmental screening tests include all of the following EXCEPT:
   a. Not administering the screen as it was intended.
   b. An assumption that the screening test done at one point in time will discover all children with every type of developmental problem.
   c. Screening tests can be time consuming for the clinician.
   d. Children are not amenable to screening between birth and three years of age.
   e. Training is necessary for the proper use of these tools.

6. When is the best age (out of the following suggestions) for a physician to administer a developmental screening tool?
   a. In utero
   b. 2 years
   c. 6 years
   d. 10 years
   e. 17 years

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Answers to questions

1.c, 2.a, 3.c, 4.e, 5.d, 6.b

Chapter I.4. Immunizations
Dennis A. Conrad, MD

A four year old boy presents to your office for the first time with a chief complaint of deficient immunizations. His mother, who in prior generations would have been characterized most accurately as an aging hippie, tells you, "He needs his shots to get into school, and he doesn't have any." You confirm that he has not received a single immunization prior to this time. When you ask why he hasn't been immunized, his mother replies that she "hasn't gotten around to it yet," and furthermore, that she "read on the Web and saw on TV that vaccines can hurt you." She then inquires of you, "What shots does a kid actually need, what are vaccines actually made of, and how safe are those immunizations, anyway?"

You perform a physical examination that reveals a healthy boy who is height and weight proportionate and developmentally appropriate for age, has no evidence of concomitant illness, and no abnormal findings upon thorough evaluation.

You then roll your eyes, sigh, and tell your nurse to reschedule your afternoon appointments. You attempt to address the mother's questions and concerns. Following your informative and comprehensive discourse, you obtain informed consent from the mother, then immunize the child using an accelerated schedule to "catch-up" the deficient immunizations. The child tolerates the vaccines without any significant adverse event occurring. After having been provided the remaining required immunizations during subsequent office visits, he begins school the autumn of his 5th year of life protected from vaccine-preventable diseases and meeting the statutory requirements for school entry. He does not acquire a vaccine-preventable disease throughout the remainder of his full and successful life as a professional surfer.

Immunizations children routinely receive currently during childhood are those that protect against hepatitis B, diphtheria, pertussis, tetanus, polio, Haemophilus influenzae type b, Streptococcus pneumoniae, measles, mumps, rubella, and varicella (1). In addition, selected populations receive immunization to protect against hepatitis A and seasonal influenza viruses. The number and ages of administration for these vaccines differ, but the goal of the recommended schedule for childhood immunizations is to provide full protection against vaccine-preventable diseases.

Immunization policy has established the practice of universal childhood immunization to provide vaccines at a time (childhood) an individual is more likely to have contact with health care providers (to increase convenience and minimize delivery costs), to protect children from vaccine-preventable diseases, to establish the foundation for an immune adult population, and to have a enforcement mechanism in order to ensure compliance (required for school entry).

Hepatitis B virus (HBV) vaccine is a recombinant subunit vaccine containing purified Hepatitis B surface antigen, synthesized by insertion of a plasmid encoding for the Hepatitis B surface antigen protein into baker's yeast (2). Hepatitis B vaccine exists as monovalent vaccine (RecombivaxHB, Engerix-B), in combination with Haemophilus influenzae type b vaccine (Comvax), and in combination with Hepatitis A vaccine (Twinrix).

The monovalent Hepatitis B vaccines are administered as a 3 dose series, with the first dose given between birth and 2 months of age, the second dose between 2 months and 4 months of age, and the third dose between 6 months and 18 months of age. Comvax should not be given before 6 weeks of age due to the Haemophilus influenzae type b component, and Twinrix is not yet approved in the United States for use in persons less than 18 years old.

Universal immunization of infants with hepatitis B vaccine is recommended to provide global protection of that birth cohort against hepatitis B infection, to provide vaccine at a time health care visits are otherwise being made, and to afford protection to infants born to mothers who have chronic hepatitis B infection. If hepatitis B vaccination is not provided in infancy at the recommended ages, then at least a 1 month interval should separate administration of the first and second vaccine doses, and at least a 5 month interval should separate the second and third vaccine doses.

The most common adverse reactions to hepatitis B immunization are fever and local reactions at the injection site. Allergic reactions occur infrequently. No causal association with multiple sclerosis or sudden infant death syndrome has been demonstrated.

Diphtheria (D; d) vaccine is a toxoid vaccine that provides formalin-inactivated diphtheria toxin, derived from a potent exotoxin produced by Corynebacterium diphtheriae (3). A "toxoid" is a denatured (nonpathogenic) toxin which stimulates an immune response against the toxin but not necessarily the organism as a whole. Immunization promotes an antibody response that neutralizes the exotoxin, protecting against the cardiotoxic and neurotoxic effects of the exotoxin which is produced during infection. Diphtheria toxoid is combined with tetanus toxoid in a pediatric (DT) and adult (dT) formulation that differs by amount of diphtheria antigen. Diphtheria and tetanus toxoids are also combined with acellular pertussis vaccine (DTaP) for use during routine childhood immunization.

DTaP is given by intramuscular injection as a primary 3 dose series at 2 months, 4 months, and 6 months of age, and as a 2 dose booster series at 12-18 months and 4-6 years. A reduced diphtheria-antigen adult formulation booster (dT) is administered at 11-12 years, and subsequent boosters are then administered at 10 year intervals throughout life.

Tetanus (T) vaccine is a toxoid vaccine that provides formalin-inactivated tetanus toxin, derived from the neuromuscular toxin tetanospasmin produced by Clostridium tetani (3). Immunization promotes an antibody response that neutralizes the toxin. Tetanus vaccine may be monovalent (TT), or combined with either diphtheria toxoid (DT or dT) or with diphtheria toxoid and acellular pertussis (DTaP).

Persons who sustain injuries more likely to become infected with Clostridium tetani (crush wounds with devitalized tissue, deep puncture wounds, wounds contaminated with soil or vegetative matter) should receive a booster dose of tetanus vaccine if at least 5 years have passed since last receiving a tetanus vaccine booster. The most common adverse reactions to tetanus immunization are fever and local reactions at the injection site. Severe allergic reactions, Guillain-Barre syndrome, and brachial neuritis occur rarely.

Three acellular pertussis (aP) vaccines are currently licensed and available for use in the United States (Tripedia, Infanrix, Daptacel). These vaccines are called acellular, to distinguish this formulation from the older whole-cell pertussis vaccine. Whole-cell pertussis vaccine consisted of inactivated ("killed") but otherwise complete Bordetella pertussis bacteria. Administration provided protection against disease but was associated with the potential for adverse effects that occurred frequently and could be quite severe on rare occasion. In order to provide a vaccine that was better tolerated, individual bacterial components that contributed to organism virulence and pathogenicity were identified and purified as individual cell-free (acellular) antigens that comprise the current acellular pertussis vaccines (3,5).

DTaP is given by intramuscular injection as a primary 3 dose series at 2 months, 4 months, and 6 months of age, and as a 2 dose booster series at 12-18 months and 4-6 years. Whole-cell pertussis vaccine was not provided to persons beyond 7 years old, due to the

increased incidence of adverse reactions associated with immunization. Currently, acellular pertussis vaccine is not recommended for immunization of persons older than 7 years of age due to the prior experience of whole-cell pertussis vaccine in this age group, although research is currently being conducted to see if adults may safely receive booster doses of the less reactogenic acellular pertussis vaccine to enhance and extend immunity to pertussis.

The most common adverse reactions to acellular pertussis immunization are fever and local reactions at the injection site. Allergic reactions occur infrequently. Rare but potentially serious reactions, including high fevers, prolonged crying, hypotonic-hyporesponsive episodes, and seizures have occurred, but at significantly lower frequency than was true for whole cell pertussis vaccine.

Inactivated polio vaccine (IPV) is a trivalent killed virus vaccine (Salk vaccine; IPOL) that contains formalin-inactivated poliovirus 1, poliovirus 2, and poliovirus 3, which are the three neurovirulent strains. Improvement in manufacturing techniques has enhanced the immunogenicity of inactivated polio vaccine (eIPV). Immunization effectively protects against paralytic poliomyelitis, but may not protect against subclinical enteric infection due to lack of secretory antibody response to inactivated polio vaccine (6).

Inactivated polio vaccine is administered as a 4 dose regimen by intramuscular injection at 2 months, 4 months, between 6 months and 15 months (3 dose primary series), and between 4 years and 6 years of age (booster dose). The most common adverse reactions to inactivated polio immunization are fever and local reactions at the injection site. Allergic reactions occur infrequently. Inactivated polio vaccine cannot cause vaccine associated paralytic poliomyelitis.

A second formulation of polio vaccine, trivalent oral live attenuated polio vaccine (tOPV; Sabin vaccine; Orimune), also provides protective immunity against paralytic poliomyelitis. In addition, oral polio vaccine uniquely protects against enteric infection by promoting mucosal immunity and offering the benefit of herd immunity by secondary immunization of susceptible persons exposed to asymptomatic shedding of vaccine strain virus from vaccine recipients. Unfortunately, as paralytic poliomyelitis due to wild-type virus was eradicated in the United States by effective immunization programs, the rare risk of paralytic poliomyelitis due to vaccine strain virus (3 to 12 cases annually) ultimately has become greater than the risk due to wild-type poliovirus. Therefore, only inactivated polio vaccine is used in the United States currently, whereas the effective, economically favorable, convenient trivalent oral polio vaccine continues to be used in wild-virus polio endemic regions in an attempt to eradicate paralytic poliomyelitis worldwide.

A vaccine containing DTaP, HBV, and IPV (Pediarix) has recently been licensed for use in the United States to provide the primary series of immunizations (first 3 doses) for children 6 months to 7 years old. This combination vaccine may be used for all 3 vaccine doses, or used to complete the primary series in infants who have already received 1 or 2 doses of DTaP, HBV, or IPV. The combination vaccine was developed to reduce the number of injections infants receive during routine childhood immunization, and provides the same vaccines that have previously existed individually (Infanrix, IPV, and Engerix-B).

Haemophilus influenzae type b (Hib) vaccine is a conjugated vaccine containing the Haemophilus influenzae type b capsular polysaccharide polyribosylribitol phosphate (PRP), which is the major virulence factor, conjugated with a carrier protein to enhance immunogenicity (7). Infants less than 6 weeks old should not be exposed to vaccines containing Haemophilus influenzae type b PRP antigen, as premature exposure may create immune tolerance, causing suboptimal antibody response upon subsequent antigen exposure and resulting in failure to develop protective antibody concentrations.

The four monovalent conjugated Haemophilus influenzae type b vaccines currently available are differentiated by their respective carrier proteins. Infants receive either a 2 dose or 3 dose series of Haemophilus influenzae type b vaccine during the first year of life (predicated by specific vaccine brand utilized), and a single booster dose between 12 months and 15 months of age (resulting in either a 3 dose or 4 dose regimen to completely immunize the child).

The number of conjugated Haemophilus influenzae type b vaccine doses required to immunize older children not receiving vaccine in infancy diminishes due to brisker antibody response seen when older children receive conjugated Haemophilus influenzae type b vaccine. If the first dose of vaccine is not administered until the child is between 7 months and 11 months of age, then only 3 doses are required to complete the regimen. If the first dose of vaccine is not administered until the child is between 12 months and 14 months of age, then only 2 doses are required to complete the regimen. If the first dose of vaccine is not administered until the child is between 15 months and 59 months of age, then only a single dose is required to complete the regimen. Non-immunized children 5 years old and older do not require Haemophilus influenzae type b vaccine unless they possess underling risk factors (impairment in immunity) that would increase their risk for invasive disease.

The most common adverse reactions to conjugated Haemophilus influenzae type b immunization are fever and local reactions at the injection site. Allergic reactions occur infrequently.

Conjugated Streptococcus pneumoniae (PCV) vaccine is a conjugated heptavalent vaccine (Prevnar) containing the capsular polysaccharides of the 7 strains of Streptococcus pneumoniae responsible for 80% of all cases of invasive pneumococcal disease occurring in children in the United States (8). Each specific polysaccharide is conjugated with a nontoxic mutant diphtheria toxin to enhance immunogenicity when administered to infants. Capsular polysaccharide is an important virulence factor for Streptococcus pneumoniae, existing in antigenically distinct permutations that confer type specificity to the individual bacterium, and requiring a type-specific host immune response to protect against disease.

Nonconjugated pneumococcal polysaccharide vaccine (PPV), which was developed before conjugated pneumococcal vaccine, currently exists as a 23-valent vaccine (PNU-IMUNE 23 and Pneumovax 23) that protects against 85-90% of strains causing invasive disease occurring in children and adults in the United States, but is poorly immunogenic in children under 2 years of age. Use of nonconjugated polysaccharide vaccine is indicated for persons at least 2 years of age, and is administered as a single intramuscular injection. Persons at high risk for invasive pneumococcal disease (asplenia, sickling hemoglobinopathy, congenital and acquired immunodeficiency, immunosuppression, spinal fluid leak, chronic cardiac, pulmonary, hepatic, or renal disease) should receive a second dose of unconjugated pneumococcal polysaccharide vaccine, administered between 3 years and 5 years following the initial dose.

Infants receive a 4 dose regimen of conjugated pneumococcal vaccine. The primary series is administered by intramuscular injection at 2 months, 4 months, and 6 months of age, and a fourth (booster) dose is administered between the ages of 12 months and 15 months. The number of conjugated pneumococcal vaccine doses required to immunize older children not receiving vaccine in infancy is reduced due to the brisker antibody response seen when older children receive conjugated pneumococcal vaccine. If the first dose of vaccine is not administered until the child is between 7 months and 11 months of age, then only 3 doses are required to complete the regimen. If the first dose of vaccine is not administered until the child is between 12 months and 23 months of age, then only 2 doses are required to complete the regimen. Routine conjugated pneumococcal vaccination is not recommend for children who are 2 years or older, although children of this age group who are at high risk for invasive pneumococcal disease should be vaccinated with the nonconjugated 23-valent PPV.

The most common adverse reactions following conjugated Streptococcus pneumoniae immunization are fever and local reactions at the injection site. Allergic reactions occur infrequently. Occasionally, fever may be high and local reactions severe, especially with subsequent doses of vaccine. Febrile seizures may complicate vaccine induced fevers.

Measles (Me) vaccine is an attenuated live virus vaccine that causes subclinical infection following administration, provoking a host immune response that protects against subsequent infection following exposure to wild-type virus. The first measles vaccine developed was a killed virus vaccine, which was associated with the potential development of an infection called "atypical measles" when vaccinated individuals were subsequently infected with wild-type virus. The current monovalent attenuated live virus vaccine (Attenuvax) contains the Moraten ("more attenuated") strain of measles virus, which effectively confers immunity while reducing the incidence of adverse events following vaccination (9).

Measles vaccine is most commonly administered in combination with mumps vaccine and rubella vaccine (MMR, mumps and rubella vaccines are also live attenuated virus vaccines), given as a subcutaneous injection to children between the ages of 12 months and 15 months of age. Approximately 95% of vaccine recipients respond to a single dose of vaccine; however, due to an increase in wild-type measles observed in vaccine recipients during the 1980s, current recommendations require a second dose of vaccine, generally administered between the ages of 4 years and 6 years prior to school entry (9).

The most common adverse reactions to MMR immunization are fever and local reactions at the injection site. Occasionally, transient rashes and transient thrombocytopenia may occur. Allergic reactions occur infrequently. Encephalitis has been suggested as an extremely rare complication of measles immunization, but definitive proof is lacking. No valid scientific evidence supports measles vaccine as causal causation for autism despite sensational claims to the contrary. Orchitis and parotitis have been rarely reported from mumps vaccine. Occasionally, transient arthralgia/arthritis and peripheral neuritis may occur from rubella vaccine (9).

Varicella (V) vaccine is an attenuated live virus vaccine that causes subclinical infection following administration, provoking a host immune response that protects against subsequent infection following exposure to wild-type virus. Oka strain varicella virus was initially developed in Japan. This strain was subsequently modified and is currently used in the United States. Varicella vaccine exists as monovalent vaccine (Varivax), which is administered as a single subcutaneous injection for children 12 months through 12 years of age, and as a two dose regimen separated by an interval of at least 4 weeks for children 13 years old and older. A single dose of varicella vaccine is associated with a 97% seroconversion rate in children <13 years old and a 94% seroconversion rate in older persons. A second dose of vaccine in associated with 99% seroconversion in adolescents and adults. Young children should routinely receive varicella vaccine as a component of universal childhood immunization, and older children and adolescent who have not had chickenpox should be identified and immunized (10,11).

The most common adverse reactions to varicella immunization are fever and local reactions at the injection site. Occasionally, recipients may have a localized (at the injection site) or more generalized varicella-like rash due to vaccine strain virus. A minority of vaccine recipients may have a mild case of chickenpox ("breakthrough chickenpox") due to wild-type virus following exposure to naturally occurring disease. Allergic reactions occur infrequently.

Hepatitis A virus (HAV) vaccine is a killed virus vaccine (12) containing formalin-inactivated hepatitis A virus that exists as monovalent vaccine and as bivalent vaccine in combination with hepatitis B vaccine (Twinrix). The first dose of vaccine produces protective antibody response within two weeks following administration. A second dose is administered to provide long term, durable protection against disease. The pediatric formulation of hepatitis A vaccine is indicated for use in the age group 2 years through 18 years. The initial dose is administered by intramuscular injection, followed by a second dose administered between 6 months and 12 months following the first.

Routine childhood immunization with hepatitis A vaccine is recommended for those regions and states where the incidence of hepatitis A infection is at least twice the national average, occurring at a frequency of at least 20 cases per 100,000 population annually. Eleven states surpass this threshold: Alaska, Arizona, California, Idaho, Nevada, New Mexico, Oklahoma, Oregon, South Dakota, Utah, and Washington. Childhood immunization with hepatitis A vaccine should be considered for those regions and states where the incidence of hepatitis A infection exceeds the national average and occurs at a frequency of between 10 and 20 cases per 100,000 population annually. Six states meet this criterion: Arkansas, Colorado, Missouri, Montana, Texas, and Wyoming. Hepatitis A immunization is also recommended for community control of recent outbreaks of infection, for travelers to hepatitis A endemic areas, for persons who have chronic liver disease, for homosexual and bisexual men, for injectors of illicit drugs, and for individuals with clotting factor disorders. The most common adverse reaction to hepatitis A immunization is a local reaction at the injection site. No serious adverse reaction is associated with hepatitis A vaccine.

Influenza vaccine is a vaccine that exists as an inactivated whole virus vaccine (not currently available in the United States) or as a split virus vaccine (subvirion vaccine; purified surface antigen vaccine) that contain the hemagglutinins of the predominately circulating strains of influenza virus. The vaccine traditionally contains antigens from two influenza A virus strains and one influenza B virus strain, determined by those most frequently isolated at the end of the current year's respiratory virus season and predicted to predominate in the next respiratory virus season. The vaccine is formulated and administered annually to compensate for antigenic shifts that occur in virus isolates in order to enhance strain-specific immunity during the current respiratory virus season. Those who should receive annual immunization include health care workers and others who may be significant vectors for contagion, healthy persons 50 years old or older, persons with underlying diseases (pulmonary, cardiac, metabolic, renal, and hemoglobinopathies), individuals receiving immunosuppression or chronic aspirin therapy, and pregnant women (beyond the first gestational trimester). Children between the ages of 6 months and 23 months should be immunized annually due to increased morbidity of influenza infection in this age group (13). Children younger than 9 years old receiving influenza vaccine for the first time should receive two doses of split virus vaccine administered in the age appropriate volume separated by at least a one month interval in order to enhance immunologic response and protection against infection.

In 2003, a live attenuated, cold-adapted trivalent viral influenza vaccine (FluMist) prepared by viral reassortment was approved for use in the United States. The vaccine exists as a spray for intranasal instillation, and contains the same three strains of influenza virus that are present in the current parenteral vaccine formulation. Use is limited to healthy individuals 5 to 49 years of age. Children 5 to 8 years old not previously immunized receive two doses of intranasal vaccine administered 60 days apart. Children 5 to 8 years old previously immunized with the intranasal vaccine, and all persons 9 to 49 years of age receive a single vaccine dose annually.

The most common adverse reactions to influenza immunization are fever and local reactions at the injection site. Allergic reactions occur infrequently. Guillain-Barre syndrome is a rare complication of influenza vaccination, apparently limited to adults.

Table 1: Recommended Childhood (Prior to School Entry) Immunization Schedule 2002 (1)
Vaccine (Route of Administration): Ages of Administration
HBV (IM): 0-1m, 1-4m, 6-18m
DTaP (IM): 2m, 4m, 6m, 15-18m, 4-6y
IPV (IM or SQ): 2m, 4m, 6-18m, 4-6y
Hib (IM): 2m, 4m, (6m), 12-15m
PCV (IM): 2m, 4m, 6m, 12-15m
MMR (SQ): 12-15m, 4-6y
Varicella (SQ): 12-15m
HAV (IM): 2-3y, 3-4y
Influenza (IM): 6-23m (annually)

Table 2: Recommended Childhood (Catch-Up) Immunization Schedule (12m-7y) 2002 (14)
Interval: Vaccines
0 (First visit): HBV, DTaP, MMR, Hib (12-60m)
1m: HBV, DTaP, IPV, Varicella
2m: DTaP, IPV, Hib (if first dose at 12-15m)
8m: HBV, DTaP, IPV
At age 4-6y: DTaP, IPV, MMR

Table 3: Recommended Childhood (Catch-Up) Immunization Schedule (7y-12y) 2002 (14)
Interval: Vaccines
0 (First visit): HBV, dT, MMR, IPV
2m: HBV, dT, MMR, IPV, Varicella (if susceptible)
8m: HBV, dT, IPV

Active immunization (as opposed to passive immunization) with vaccines provokes a host response that potentially confers durable immunity and protects against subsequent infection and disease following exposure to naturally occurring infection.

In the special circumstance of a susceptible person requiring immediate protection against disease, either prior to or following exposure to infection, transient immunity may be conferred by passive immunization, where preformed protective antibodies are administered. The advantages of passive immunization is the potential to provide immediate protection to the host. The major disadvantage of passive immunity is the subsequent decay of passively acquired antibody by metabolism and elimination, ultimately rendering the host potentially susceptible to infection once passively acquired antibody titers fall to subprotective concentrations.

Active immunization utilizes a live or killed antigen to stimulate the immune system to form an active immune response, while passive immunization is merely the injecting or infusing human or animal-derived antibodies into the body. Passive immunization preparations currently available include serum immunoglobulin, existing in formulations for intramuscular (IM-IG) and intravenous administration (IVIG), which can provide global protection against infections that are prevalent in the populations from whom these products are derived. In fact, this is why the administration of attenuated live virus vaccines (measles, mumps, rubella, varicella) is deferred for persons who have recently received blood products (including immunoglobulin preparations), since passively acquired antibody may prevent the vaccine-induced subclinical infection and the active immune response from developing. Killed virus, toxoid, conjugated polysaccharide, recombinant subunit, and bacterial antigen vaccines are not as adversely affected by the presence of passively acquired antibodies, and thus may be administered without consideration of blood products (including immunoglobulin preparations) recently received by the potential vaccine recipient.

Passive immunization products may also be specific for selected infections. These agents are labeled "hyperimmune" because effective concentrations of neutralizing antibody have been specifically ascertained. Those diseases for which passive immunity may be provided include respiratory syncytial virus (RSV-IG), palivizumab ("humanized" murine monoclonal anti-RSV antibody), hepatitis B (hepatitis B immune globulin, called HBIG), varicella (varicella zoster immune globulin; called VZIG), cytomegalovirus (cytomegalovirus immune globulin), and rabies (rabies immune globulin). Passive immunization products that protect against virulent toxins associated with infection are often called "antitoxin", and are administered to mitigate the significant systemic toxicity associated with infection. Tetanus immune globulin is derived from human serum. Botulism antitoxin (trivalent against botulism toxins A, B, and E) and diphtheria antitoxin are derived from horse serum (15).

Attenuated live virus vaccines (measles, mumps, rubella, varicella) should not be administered to persons who have impairment in immunity (congenital or acquired immunodeficiency, receiving immunosuppressive therapy, have malignancy or have undergone bone marrow or organ transplant) or are pregnant, due to the potential risk for the expected subclinical infection following immunization to become clinical, and potentially severe, posing risk to the vulnerable host or unborn child. Moreover, attenuated live virus vaccines should be administered simultaneously (during the same office visit), or individually separated by an interval of at least 4 weeks to prevent immunological interference with the second vaccine. Note specifically that attenuated live virus vaccines can be given simultaneously or at least 4 weeks apart, but at no time between these two time points. Additional doses of attenuated live virus vaccines in excess of those recommended for childhood immunization may be administered without increased risk of adverse reactions (16).

Noninfectious vaccines (killed virus, recombinant subunit, toxoid, conjugated polysaccharide, bacterial antigen) may be administered to persons who have impairment in immunity without increased risk, since these vaccines are incapable of causing infection. Immunologically impaired hosts may have suboptimal response to these vaccines, and may not be protected against subsequent development of disease following exposure. Noninfectious vaccines may be administered simultaneously or separated at any interval without appreciable risk of impaired immunologic response (16). Additional doses of these vaccines in excess of those recommended for childhood immunization are generally well tolerated, although the risk for enhanced systemic and local reactions may increase. Whole cell pertussis vaccine, diphtheria vaccine, and pneumococcal polysaccharide vaccine may be particularly prone to provoke exaggerated reactions with excessive doses of vaccine.

Vaccines are the single most cost-effective interventions performed to improve and maintain the health of citizens of the United States, and have been cited as one of the most significant advancements in medical practice occurring during the 20th century (17). Vaccines are not without risks, but the anxiety expressed by some parents is almost always the result of misperceptions fueled by misinformation. When considered against the risk of infection with concomitant associated morbidity and mortality, the benefits of universal childhood immunization far outweigh all risks for each of the vaccine-preventable diseases. In those circumstances where rare but potentially serious adverse reactions to immunization are demonstrated, such as the risk for intussusception following administration of the oral tetravalent rotavirus vaccine (18), the national Vaccine Adverse Event Reporting System (VAERS) provides identification of these rare complications and promotes the appropriate corrective actions. Health care providers should strongly endorse routine childhood immunization, and be capable and willing to adequately address any parental concerns.

Questions

1. Which of the following vaccines would be contraindicated in a 4 year old boy receiving immunosuppressive therapy for autoimmune hepatitis?
    a. Hepatitis A vaccine
    b. Hepatitis B vaccine
    c. Acellular pertussis vaccine
    d. Inactivated polio vaccine
    e. Varicella vaccine

2. Which vaccine should not be given to an 8 year old girl who has not been immunized previously?
    a. Hepatitis B vaccine
    b. Tetanus vaccine
    c. Acellular pertussis vaccine
    d. Inactivated polio vaccine
    e. Measles vaccine

3. Which parenteral vaccine should not be characterized as an attenuated live virus vaccine?
    a. Influenza vaccine
    b. Measles vaccine
    c. Mumps vaccine
    d. Rubella vaccine
    e. Varicella vaccine

4. Which passive or active immunization is specifically recommended for women in the second or third trimester of pregnancy?
    a. Respiratory syncytial virus immune globulin
    b. Cytomegalovirus immune globulin
    c. Rubella vaccine
    d. Influenza vaccine
    e. Varicella vaccine

5. Increased risk for intussusception was observed as a rare complication following immunization with which vaccine?
    a. Inactivated polio vaccine
    b. Oral polio vaccine
    c. Rotavirus vaccine
    d. Hepatitis A vaccine
    e. Hepatitis B vaccine

6. Indicate whether the follow are examples of active or passive immunity:
    a. palivizumab
    b. Diphtheria-Tetanus toxoid
    c. Diphtheria immune globulin
    d. MMR
    e. Influenza vaccine
    f. Botulism antitoxin

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Answers to questions

1.e

2.c

3.a. It should be noted that the current parenteral influenza vaccine is not a live attenuated virus. However, a non-parenteral intranasal live attenuated influenza vaccine is available.

4.d

5.c

6a.passive

6b.active

6c.passive

6d.active

6e.active

6f.passive

Chapter I.5. Hearing Screening
Teresa Han Seo

A 2 year old female presents to your office with her mother who is concerned that unlike her other children, her youngest daughter is not talking. Her child has a very limited vocabulary consisting of only word fragments such as "ma." She interacts with her parents and older siblings by grunting and pointing to objects. She cries when she does not get her way. Her mother has recently noticed that her daughter seems to ignore her unless she looks straight at her while speaking. Her mother feels that her child is otherwise normal since she likes to watch cartoons and play with dolls. Her child's past medical history is significant for numerous middle ear infections. Her immunizations are all up to date. Her birth history is normal.

Exam: VS T 37, HR 120, RR 24, BP 90/60. Height 89 cm (35 in) (75%ile), weight 13.2 kg (29 lbs) (75%ile). She appears well, in no acute distress. Her eyes are normal. Her tympanic membranes in both ears show some scarring and thickening. Oral mucosa is moist. Neck is supple without adenopathy. Heart regular. Lungs are clear. Abdomen is soft and non-tender. She is shy, so her speech is difficult to assess. A neurologic examination finds no abnormalities. She has age appropriate gross motor and fine motor skills.

Based on the history reported by her mother, you recommend that she undergo comprehensive audiology testing which reveals a bilateral moderate conductive hearing deficit attributed to repeated episodes of otitis media. Possible considerations at this point include: 1) Surgical tympanostomy tubes if she continues to have frequent episodes of otitis media. 2) Hearing aids with speech and audiology therapy sessions followed by special education preschool if language milestones are not age appropriate by the time she is 3 years of age.

The most critical period for the development of hearing and speech occurs in the first 6 months of life. Moderate to severe hearing impairments, as well as mild or unilateral hearing deficits, during the first year of life are known to affect speech, language, cognitive and behavioral development in children. In infants younger than 6 months of age, early intervention is thought to improve the development of speech, language, and cognition, which in turn, decreases the need for special education (1). Deafness is more prevalent than any other disabling condition for which mandated neonatal screening programs exist (2).

Each year, approximately 5000 infants are born in the United States with moderate to profound, bilateral permanent hearing loss (3). The prevalence of moderate to profound hearing impairment in newborns, including sensorineural (SNHL) and conductive hearing loss (CHL), is approximately 1 to 3 per 1,000. There is an approximate 2-fold increase in this number when infants with mild SNHL are included (1).

The prevalence of hearing impairment increases considerably in newborns that have any of the following risk factors as described by the Joint Committee on Infant Hearing, Year 2000 Position Statement (1,4):

- An illness or condition requiring admission of 48h to a neonatal ICU.
- Stigmata or other findings associated with a syndrome known to include a sensorineural or conductive hearing loss.
- Family history of permanent childhood sensorineural hearing loss.
- Craniofacial abnormalities, including those that have morphologic abnormalities of the pinna and ear canal.
- In utero infection, such as cytomegalovirus (CMV), herpes, toxoplasmosis, or rubella.

The Joint Committee on Infant Hearing, Year 2000 Position Statement also illustrates specific risk indicators associated with progressive or delayed-onset hearing loss (1,4):

- Parental or caregiver concern regarding hearing, speech, language, or developmental delay.
- Family history of permanent childhood hearing loss.
- Stigmata or other findings associated with a syndrome known to include a sensorineural or conductive hearing loss or Eustachian tube dysfunction.
- Postnatal infections associated with a sensorineural hearing loss, including bacterial meningitis.
- In utero infection, such as CMV, herpes, toxoplasmosis, rubella, or syphilis.
- Neonatal indicators, specifically hyperbilirubinemia at a serum level requiring exchange transfusion, persistent pulmonary hypertension of the newborn associated with mechanical ventilation, and conditions requiring the use of extracorporeal membrane oxygenation.
- Syndromes associated with progressive hearing loss (i.e., neurofibromatosis, osteopetrosis, Usher syndrome)
- Neurodegenerative disorders (i.e., Hunter syndrome) or sensory motor neuropathies (i.e., Friedreich's ataxia, Charcot-Marie-Tooth syndrome)
- Head trauma.
- Recurrent or persistent otitis media with effusion for at least 3 months.

Neonatal Hearing Screening

Sensitive techniques are available for performing neonatal hearing screening, and early intervention has been shown to positively affect language development in hearing impaired children (2). Prior to the mandate of universal newborn hearing screening (UNHS) programs in at least 32 states in the United States, the average age that children were diagnosed with hearing impairments was approximately 30 months. Children who had mild or moderate hearing losses often were not identified until entering school. Studies have shown that even targeted screening of high-risk groups can identify only up to 50% of children who have significant hearing impairments prior to the development of speech (1).

Initial screening for hearing deficits is conducted within the hospital following the birth of a newborn and depending on the results, additional screening may be implemented prior to or following discharge. Currently utilized screening methods include automated auditory brainstem response (AABR), transient evoked otoacoustic emissions (TEOAE), and distortion product otoacoustic emissions (DPOAE). These methods incorporate a device that objectively and automatically detects one's response to sound presented as an evoked potential or an otoacoustic emission. These screening techniques reveal whether specific stimulus levels elicit a response. These screening tests are unable to provide a quantitative estimate of the severity of the hearing deficit and cannot distinguish SNHL from CHL (1). The auditory brainstem response (ABR) test (also known as brainstem auditory evoked response-BAER), which is an electrical waveform or an evoked potential (similar to electroencephalography) produced by auditory nerve and brainstem activity following a click or other brief sound. ABR testing is independent of behavior and is influenced by the intensity and rate of stimulation. The presence of an ABR indicates that sound is perceived by the test subject. Abnormal ABR patterns have been shown to correlate with hearing deficits and

enables the differentiation between CHL and SNHL. Like any test, the validity, efficiency and test result interpretation is a function of the test administrator's skill and experience (1).

The transient evoked otoacoustic emissions (TEOAE) and distortion product otoacoustic emissions (DPOAE) both work on the principle in which a sound stimulus (such as a click) causes the cochlea to form an emission. This emission can be detected by placing a microphone in the ear canal connected to a computer specially designed to analyze this emission.

The current American Academy of Pediatrics guidelines recommend that hearing deficits are identified by 3 months of age and intervention initiated by 6 months of age (1). A review by Clemens and Davis (5) reports that the false-positive rates of previously reported UNHS (universal newborn hearing screening) programs range between 2.5 and 8%. Higher false-positive rates may lead to a variety of unnecessary negative effects, including emotional trauma, disease labeling, iatrogenic adverse events from unnecessary testing, and increased expense in terms of time and money. Clemens and Davis have shown that simply rescreening all infants who failed their initial UNHS before hospital discharge reduced the false-positive rate to 0.8% (5). Sokol and Hyde report that a maximum false-positive rate of 3% is generally acceptable for hearing screening programs (1). It is important to recognize that screening tests in high- and low-risk groups will yield different results due to variation in the presentation and distribution of hearing disorders within these groups and the fact that it is easier to achieve ideal testing conditions and results in babies who are sleeping, less distressed, and in low-risk groups (1).

There are some disadvantages with the UNHS programs. Sokol and Hyde's review (1) indicates that it is important that UNHS programs include follow-up of those infants who fail in-hospital screening or are not successfully screened before discharge due to shorter hospital stays and/or poor compliance with following-up on those who fail the first screen. One should also note that passing a UNHS program does not automatically indicate that an infant has normal hearing. Furthermore, acquired hearing disorders due to congenital (i.e., CMV) or acquired infections (i.e., meningitis), acquired conductive hearing impairment (due to recurrent otitis media infections), or auditory neuropathy will not be detected by UNHS programs (1).

UNHS programs have enabled earlier identification, diagnosis, and intervention of hearing deficits in infants. Sokol and Hyde's report (1) suggest that early intervention improves speech, language, cognition, and social skills through the use of interventions such as hearing aids and cochlear implants (1).

Post-Neonatal (older ages) Hearing Screening

Approximately 5-10% of newborns will display one of the risk factors for progressive or late-onset hearing loss described by the Joint Committee on Infant Hearing (1,4). Sokol and Hyde (1) suggest that infants who are at risk for developing hearing loss that manifests after neonatal screening (i.e., perinatal CMV infection) should be rescreened every 3 to 6 months for at least 3 years. (1,4).

Other conditions that may affect hearing including bacterial meningitis or head injury, should also be evaluated appropriately using screening methods such as DPOAE (distortion product otoacoustic emissions), TEOAE (transient evoked otoacoustic emissions), or the more accurate AABR (automated ABR screening) test. Postnatal screening failures should be followed up by full comprehensive audiologic and otologic examination.

Some of the best tests for evaluating hearing deficits in infants older than 6 months of age includes behavioral tests such as visual reinforcement audiometry (VRA) which evaluates one's response to specific tones projected within a soundproof room from various locations. VRA can accurately evaluate children 6 months of age and older who have normal neurological development. The reliability and accuracy of behavioral tests are limited in infants who are younger than 6 months of age or have developmental delays or certain physical disabilities (1).

The behavior of the child and environmental noise levels may affect the results of hearing screening in infants. OAE and AABR testing are most accurate when the child is preferably sleeping or resting quietly, which can be difficult in children greater than 6 months of age. If this is not possible, mild sedation or light general anesthesia may provide a better testing environment in these children (1). For children older than 6 months of age without cognitive impairments, behavioral screening by VRA or conditioned play audiometry (CPA) is acceptable. CPA is where the child is conditioned to make a response using common play materials (e.g., being taught to drop a block into a bucket) when hearing a sound stimulus. Informal behavioral screening using noisemakers and observing a child's response is inaccurate. Evaluating children with substantial cognitive disorders is more complex and challenging and requires long-term evaluation (1).

Screening preschool-aged children under a Early Hearing Detection and Intervention program may identify preschoolers who have developed hearing deficits that have presented following birth, are progressive, or associated with diseases (i.e., meningitis) or head trauma. This impairment may hinder further development of hearing, speech and language (1). Middle ear conditions are common in 3 to 5 year old children, and it is important for health care professionals to screen for both hearing loss and middle ear problems. The objectivity of OAE screening makes it ideal for cooperative children. CPA, which has the capacity of evaluating the full perceptual system of a child, can also be used for screening cooperative, responsive 3- to 5- year olds with an experienced tester. Children who cannot perform sufficiently on CPA can be tested successfully with VRA. Screening errors can be prevented by conducting both objective and behavioral testing, where practical. Screening failures in this group should also be followed by full audiologic assessment (1).

Failing an objective screen in a child should alert health care professionals to determine whether the failure is caused by middle ear disease. Tympanometry is used to detect middle ear conditions by utilizing varied air pressures to assess the compliance of the tympanic membrane. For example, an acute otitis media will result in low compliance indicating a stiff tympanic membrane because the space behind the tympanic membrane is filled with fluid. A normal tympanogram increases suspicion for SNHL and should be followed up by a comprehensive diagnostic audiologic assessment. An abnormal tympanogram suggests that the screening failure is probably a result of a middle ear disorder. One should remember that abnormal tympanograms do not necessarily rule out a sensorineural component of hearing loss (1).

Detailed guidelines for hearing screening protocols for children are available in the Joint Committee on Infant Hearing 2000 position statement (4).

Questions

1. True/False: In infants younger than 6 months of age, early intervention for hearing impaired infants is believed to improve the development of speech, language, and cognition, which in turn, decreases the need for special education.
2. Name some in utero infections which are known to cause hearing abnormalities.
3. True/False: Current screening methods including automated auditory brainstem response (AABR), transient evoked otoacoustic emissions (TEOAE), and distortion product otoacoustic emissions (DPOAE), are able to distinguish whether a child has sensorineural or conductive hearing loss.
4. What is the best test for assessing hearing deficits in infants older than 6 months of age?

5. After failing an objective hearing screen, tympanometry testing is conducted and the results are abnormal. What does this suggest?
6. True/False: OAE and AABR methods are most accurate when the child is resting quietly or sleeping.

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Answers to questions

1. True
2. TORCH: toxoplasmosis, rubella, CMV, herpes
3. False
4. Best test for this age group: Behavioral tests that rely on operant conditioning, such as visual reinforcement audiometry (VRA) involves testing one's response to specific tones projected within a soundproof room from different locations.
5. Screening failure is attributable to middle ear disease. Yet, this does not completely rule out a sensorineural defect.
6. True

Chapter I.6. Anticipatory Guidance

Corinne C. Chan-Nishina, MD

A 2 year old male presents at a pediatrician's office for his annual physical. His mother has concerns about his appetite. He is described as a finicky eater and will not sit still at the dinner table for very long. He will occasionally eat meat. He eats vegetables, and loves rice. He also eats fruit and whole grain cereals. He drinks about two to three glasses of milk a day and maybe one glass of fruit juice per day. He has no problems with his bowel movements. She is also concerned about his temper tantrums, especially when he doesn't get his way. Spanking has not worked too well. He has difficulty sharing with his siblings. This often escalates from sibling conflicts to severe temper tantrums. She is also concerned that he is not making progress with his toilet training. He has used the toilet for both bowel movements and urination, but he will not consistently tell his mother when he has to go. His mother would also like to know when he should stop using his car seat. She has no concerns about his development. He actually seems advanced compared to his older sibling who is doing well at school. His birth and past medical history is unremarkable. His parents are happily married and there have been no remarkable changes in the household.

Exam: VS are normal. Height 90cm (75%ile), Weight 13.5kg (75%ile), Head circumference 50cm (50-75%ile). He is awake, alert and active. His head is normal. Red reflexes are present in both eyes. His pupils are equal, round and reactive to light. Extraocular movements are intact. The cover test is negative. The tympanic membranes are without erythema. There is a good light reflex bilaterally. The nares are clear and without discharge. Oropharynx is moist and pink without erythema, exudates or other lesions. There are multiple dental caries present. There are about twenty teeth. They are cream colored and have plaque present. His neck is supple without lymphadenopathy. His heart and lungs are normal. His abdomen is soft and nondistended without organomegaly or masses. There are normal Tanner I male genitalia with testes descended bilaterally. Extremities are normal. There are no signs of scoliosis. There is no rash. However, there is a Mongolian spot to the buttocks. His neurological exam demonstrates good strength and muscle tone. DTR's are 2+ in the lower extremities. He has good coordination and a normal gait. There is also normal sensation to light touch.

There are many challenges that parents and children face today. One of four children in the U.S. currently lives in poverty. These children and families face poor nutrition, poor access to health care, violence and neglect. Many of the nation's children grow up in single parent households (1). There are many children who live with foster families because of neglect, abuse, parental substance abuse or domestic violence. These families are at particularly high risk for their children having poor physical and emotional health.

However ALL parents and caregivers with support from medical professionals have the potential for greater impact on the health and well being of their children. Pediatricians and other child health providers emphasize prevention, early detection, and management of various behavioral, developmental, and social functioning problems (2). A major aspect of preventing and managing such problems includes concise and effective discussions with parents and other caregivers; what is commonly called anticipatory guidance.

The United States Preventive Services Task Force has compiled a list of evidence based preventive health recommendations. These include risk reduction with vehicle safety seats, smoke detector use, hot water heater temperature reduction, smoking cessation, use of bicycle helmets, and child proofing the home for medications and poisons. For a number of important health related behaviors (e.g. smoking) there is good evidence from high quality studies that physicians can change patient behavior through simple counseling in the primary care setting. For many other behaviors, the effectiveness of counseling has been demonstrated only over the short term or has not been examined in appropriately designed studies (3).

The child in the case above does not have any serious physical exam findings except for dental caries. He is growing well. A pediatrician or trained medical professional can address all his mother's other concerns.

Each age group has anticipatory, behavioral and developmental issues that relate particularly to children of that age. The following are some of the important topics used in anticipatory guidance for caregivers of two year old children. The gender throughout this discussion is for a boy (as in our case above) but this discussion is completely relevant for girls also.

Nutrition: The two year old toddler is in the process of becoming more independent and separating from his primary caregiver who has nurtured and protected him. He begins to make his own choices and has the desire to do things by himself. He is more interested in play and exploring the world, and discovering how it all works. Children at this age have a difficult time sitting down for extended periods of time, and want to choose their own foods, and feed themselves.

There are ways to continue to make mealtimes pleasant and enjoyable for everyone. It is important for the toddler (and children of all ages) to have meals with his family to support the promotion of constructive family relationships and to provide role models at mealtime. Parents should encourage conversation at mealtimes, and make meals pleasant and comfortable. The TV should be turned off and reading materials should be put somewhere else. Children at this age may receive two to three nutritious snacks per day. Nutritious snacks should be rich in complex carbohydrates. Sweets and high fat snacks should be limited or avoided, since this may cause children to lose their appetite for a nutritious lunch or dinner. Juice should be limited to 4-6 ounces per day. Children can be offered a variety of nutritious foods and be allowed to choose what to eat and how much. It is perfectly normal for children at this age to eat a lot for one meal, and not much the next. Reasonable mealtime behavior should be enforced, but eating should never be forced. Eating should not become a power struggle. Children at this age like to experiment with their food (1). Good nutrition can make a big difference in how children grow, develop and learn.

Pediatric Oral Health: Dental decay (caries) is the most common chronic infectious disease of childhood. If severe enough, they may lead to malnourishment, absence from school, and low self-esteem. Pediatricians need to take a more active role in promoting good oral health and counseling parents on the importance of preventing dental disease in children. High risk children need to be identified. A brief dental screening includes oral inspection, noting the number of erupted teeth, and their color, spacing and enamel status, as well as inspection for dental caries. Those with dental caries should be referred to the dentist immediately.

Caregivers should be taught the role of diet in promoting good oral health, and those factors that can lead to dental caries. Bottles and "Sippy" cups should not be used as pacifiers. Bottles or breastfeeding at bedtime should be discouraged after the eruption of teeth. Infants should be weaned from the bottle before 15 months (10). Parents should be informed of the effects of prolonged use of high sugar liquids and foods (such as juices, sodas, and candy). High sugar medicines may also lead to dental caries. For infants, parents should be instructed to clean their mouth and teeth regularly after feedings. The pediatrician should demonstrate this whenever possible. Toddlers and preschoolers will need the help of a parent, but they can be encouraged to brush their own teeth first, before receiving help as necessary from the parent.

Physicians should prescribe and counsel parents on the use of fluoride supplements in communities without fluoridated water supplies, and on the use of fluoride toothpaste (use only a pea-sized amount or less to prevent excessive fluoride ingestion). Both of these should be kept out of the reach of children to prevent ingestion of excessive amounts of fluoride. Most importantly, pediatricians can ensure that every child has an established "dental home". It is recommended that the first visit with a dentist occur six months after the eruption of the first tooth (which is at approximately twelve months of age) (4).

Discipline: This is a topic that often comes up at the well child visit. Parents often ask pediatricians for their advice regarding appropriate and effective discipline. The word discipline comes from the root word disciplinare, which means "to teach or instruct". This refers to the system of teaching and nurturing that prepares children to achieve competence, self-control, self-direction, and caring for others (5). There are three key elements to effective discipline: 1) a learning environment characterized by positive, supportive parent-child relationships; 2) a strategy for systematic teaching and strengthening of desired behaviors; and 3) a strategy for decreasing or eliminating undesired behaviors. All of these must be present to achieve improved child behavior (3).

The developmental age of the child must be considered when choosing a form of discipline. One would not expect an infant or toddler to respond to reasoning. A two year old might respond well to the caregiver providing attention to him to increase positive behaviors. A caregiver withholding attention can decrease undesirable behaviors. Being consistent is very important. Removing or eliminating undesirable behaviors requires that the parent and child are both clear on what the problem behavior is. Once this is established, then there should be an immediate consequence when the targeted behavior occurs. An appropriate consequence should consistently be provided each time the targeted behavior occurs at this age. At older ages more sophisticated techniques may be used that delay the positive or negative reinforcers. Time-out is a form of extinction that may be used at this age. For a two year old this would consist of removing parental attention or being placed in a chair for a specified time (one minute per year of age of the child is suggested) without any adult interaction. Initially this may result in an increase in negative behavior. If the parent accepts this as a normal reaction and chooses to ignore the behavior, this will eventually result in a decrease in outbursts, as well as a decrease in the targeted behavior (6).

Caregivers should try to remain calm. Parents are more likely to use aversive techniques and punishment when they are angry, irritable, fatigued and stressed. It can be difficult to discuss discipline with parents since many will use methods with their children that were once used on them. They may be hesitant to discuss methods of corporal punishment. One good way to start the discussion is to talk about a behavior that was observed during the visit, and discuss its occurrence at home. It is important to remain non-judgmental or the conversation may become emotionally charged.

Toilet training: This topic concerns many caregivers during the toddler stage. Parents should be counseled to start toilet training when the toddler shows interest and is willing to participate. It should not become a control issue. Signs that signify readiness are: staying dry for periods of about two hours; knowing the difference between wet and dry; being able to pull their pants up and down; wanting to learn; and being able to signal when they are about to have a bowel movement. Once these signs are present, parents may want to seat their child on their potty. Caregivers should give lots of positive reinforcement for sitting and also praise when the child is successful using the potty. Making the experience a pleasant and positive one will ensure success in toileting.

Injury prevention: There is a fair amount of evidence to suggest that injury prevention counseling to parents of young children is effective (3). Every child deserves to grow up in a safe environment, and most authorities believe that counseling families in injury prevention is both effective and cost efficient. This aspect of anticipatory guidance is an essential part of the comprehensive care of infants, children and adolescents. Severe injuries are most commonly caused by motor vehicle crashes, followed by drowning, burns, choking, and falls (7). Initially the focus should be on the parents, but as the child matures, the focus should switch more to the child as they become more responsible for their own actions. Counseling on the prevention of automobile injuries should be a priority, since there is good evidence to suggest that the use of car safety seats is effective. Motor vehicle injuries are a leading cause of death and morbidity. Child safety seats can reduce serious injury by as much as 67%, and mortality by as much as 71% (8). The focus of this counseling should be on the use of approved child safety seats, and following the instruction manual on the proper installation and use.

There is also good evidence to suggest that poisoning in young children is associated with parents' lack of awareness of the treatment of poisonings (7). Parents should be given the number for the poison control center. They should be advised to not administer anything for the poisoning before calling the poison control center. Most importantly, they should be counseled on the proper storage of

medications, cleaning agents, household chemicals and toxins. Bottles for chemicals and household cleaners, or other potential toxins should not be reused for other things.

An association exists between drowning and leaving a child less than 3 years old unattended in the bathtub. Evidence that a health provider can influence parental supervision of young children during bath time is limited (9). Still, parents should be cautioned of the dangers of leaving young children unattended around water, such as the bathtub, a bucket full of water or the swimming pool. Specifically, counseling should include example points such as attending to their infant in a bathtub is more important than answering the phone or the doorbell. Parents of older children may develop a false sense of security if their children have had swimming lessons and should be cautioned that their children still need to be supervised around water, since they are still at risk for drowning.

In conclusion, there are multiple potential opportunities in the office and clinic setting for preventing injury and disease with caregiver guidance and teaching. This is true for children with and without serious medical or social issues. A complete discussion of all the elements of anticipatory guidance at each age group is beyond the scope of this chapter. The American Academy of Pediatrics provides pediatricians with recommendations on anticipatory guidance counseling at each age group (1,10).

Questions

1. True/False: For most problems caused by parental child rearing knowledge deficits, there is good evidence from high quality studies that physicians can change parental behavior through simple counseling in the primary care setting

2. True/False: The anticipatory guidance issues for two year olds are very different for boys as compared to girls.

3. In "disciplining" a two year old child, one should
   a. Punish
   b. Explain verbally at length the reason for the "disciplining".
   c. Teach or instruct.
   d. Always use positive reinforcement.
   e. Do to the child what the child does to others so they learn why not to do certain things.

4. True/False: Children can develop fluorosis by using fluoride toothpaste and fluoride supplements.

5. What is the most common cause of serious injury and death for children and teens?
   a. Falls
   b. Water-related injuries (submersions, drownings)
   c. Burns
   d. Choking
   e. Motor vehicle crashes

6. True/False: Parents do not need to supervise their two year olds who have already completed swimming lessons.

7. Which is INCORRECT about a toddler around feeding issues?
   a. Parents should encourage conversation at mealtimes.
   b. Children at this age may receive two to three nutritious snacks per day.
   c. Juice should be limited to 4-6 ounces per day.
   d. Children can be offered a variety of nutritious foods and be allowed to choose what to eat and how much.
   e. It is abnormal for children at this age to eat a lot for one meal, and not much the next.

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Answers to questions

1.False, 2.False, 3.c, 4.True, 5.e, 6.False, 7.e

Chapter I.7. Common Behavioral Problems in Toddlers and Young Children

Sharon M. Tisza, MD

A 5 year old girl named Sue is brought to the pediatrician's office with a chief complaint of temper tantrums. Her mother is frustrated and explains that Sue kicks and screams anytime she doesn't get her way. She sometimes swears and destroys things in her fits of rage. Two days ago she flailed her arms around while out of control and sustained a scratch on her forearm that bled. Her mother has tried yelling at Sue, spanking her on the buttocks, and embarrassing her in public. None of these techniques seem to work. In fact, her mother says that the harder she tries to control Sue, the worse she gets. This problem is causing difficulty especially between Sue's parents, as they don't agree on how to handle these tantrums. Sue's mother feels that they should take action immediately by confronting Sue and telling her that what she is doing is not acceptable. Sue's father would prefer to spank her several times on the buttocks and give her a lecture after sending her to her room for an hour or so. They openly disagree on how to discipline Sue, and Sue seems well aware of the difference in their parenting styles.

Exam: VS are normal. Height, weight and head circumference are at the 50th percentile. Sue is a well developed, well nourished attractive little girl in no acute distress. She comes in quietly with her mother and father and sits on the chair near her mother, looking up shyly at the examiner. No abnormalities can be identified on examination of HEENT, neck, heart, lungs, abdomen, and back. There is a healing 5 cm healing linear abrasion to her right forearm. There are multiple bruises to both anterior tibial surfaces at different stages of healing, with normal range of motion, no deformities and strength 5/5. Her neurological exam is intact.

Following this initial evaluation for temper tantrums, her mother and father return to the pediatrician weekly for the next eight weeks. They receive twenty minutes of instruction each time on behavioral problems, effective methods of discipline and child management. Her parents also keep a journal of specific instances when Sue becomes out of control and how they handle it. The tantrums become less and less frequent as time goes by and her parents become more relaxed and start to enjoy Sue again. By the end of the eight weeks, the tantrums have decreased from several times per day to once or twice per week. The tantrums are also less severe than they used to be and the recovery time is much shorter. Sue's mother and father are pleased with the results and are encouraged to return in the future if they need to discuss Sue's behavior again.

Some children seem to get through childhood without many problems at all and others seem to have an unusual amount of difficulty. Parents are often puzzled as to why their children do not behave or listen while their friend's children seem to be perfect angels. Some of the most common behavioral problems in children include temper tantrums, not following directions, whining, fighting with siblings or other children, breaking rules and talking back. Fortunately there is hope in dealing with everyday discipline problems using methods that are effective and easy to learn.

Parents have the ability to shape their children's behavior towards both good and bad results. All behaviors are shaped by rewards that are given to them. A common mistake that parents make is to accidentally reward their children's bad behavior. Four year old Jack gets to eat ice cream before dinner. He has been whining and begging for the ice cream long enough that his mother gives it to him so she can finish preparing dinner. Unfortunately, by rewarding bad behavior it is often strengthened. On the other hand behavior that is not rewarded, but instead punished, will often weaken and therefore decrease (1).

Developmentally, it is expected that young children will have a difficult time controlling their emotions, particularly if tired, hungry or stressed. Toddlers and preschoolers often lack the self-control necessary to express anger and other unpleasant emotions peacefully. When this happens it is important for the child's caregiver to be able to provide him or her with the support to deal with these difficult and uncomfortable feelings. Children learn a lot through their parents' modeling of behaviors and this is the main reason for parents needing to be most in control when their children are feeling out of control. If a father or mother joins the child in an uncontrollable emotional state, the situation will likely worsen because the child will feel less safe and more out of control (2).

Luckily for their parents, most children want to please their parents. Parents can therefore use this to their advantage when deciding how to discipline children. When a parent shows joy for a behavior that is good, the child will be positively reinforced for doing this behavior. On the other hand if a parent shows disapproval for a behavior, the child is less likely to repeat this behavior given the basic principle that children want to please their parents (3).

Discipline is the system in which parents guide and teach their children. This word is often confused with the term punishment. The purpose of discipline is to teach children the difference between right and wrong, to tolerate delayed gratification and to incorporate a sense of limits and appropriate behavior. Teaching discipline is a challenging task for parents and caregivers and not one that is taught overnight. It takes many years for most children to be able to achieve self-control. Also, as children grow and develop, so do the types of things that they must be taught. The method of discipline must grow and change with the child. Caregivers need to be flexible because of changes in children and their environment as children mature and grow (4).

Do's and Don'ts: Three Good Child-Rearing Rules to Keep in Mind

1) Reward good behavior and do it quickly and often. A child's good behavior will be positively reinforced and therefore strengthened when they receive a reward from a caregiver. Social rewards are the most effective rewards and include smiles, hugs, kisses, words or praise, eye contact and attention. Other rewards include activity rewards such as going to the park or helping to bake cookies and material rewards like ice cream, money or a compact disc. Social reward are the most powerful, easiest to give and least expensive. The other types of rewards should be used less often. It is important for parents to remember that they are the most important reward for their children. It is very important to keep in mind that especially in younger children rewards need to immediately follow the behavior.

2) Avoid accidentally rewarding bad behavior. This will strengthen the bad behavior and is a very easy trap for parents to fall into. One example is when a child whines to get their parents attention. If a parent gives the child attention while they are whining, even if this attention is to yell at their child, it will act to reward the bad behavior of whining. Parents are very prone to making this mistake, especially if preoccupied with another activity like making dinner, talking on the phone or having a long day.

3) Punish some bad behavior by using mild punishment. Examples of mild punishment include time-out, scolding, natural consequences and logical consequences.

Time-out is a very effective form of mild punishment. Time-out literally means time-out from all the things the child enjoys, for example - rewards, parent's attention, reinforcement, toys, music and all other interesting activities. Time-out has two major goals. The immediate goal is the stop the problem behavior as quickly as possible and the long-term goal is to help the child learn self-discipline. The good thing about time-out is that it does not emotionally harm the child and it models calm and good behavior on the parent's part. Time-

out works best with children age two to twelve. This method should be considered with certain types of behaviors including impulsive, aggressive, hostile and emotional behaviors. Time-out does not work to get a child to begin doing a behavior, but it is very effective in stopping bad behaviors.

Time-out can be used initially with one or two target behaviors and once the parent and child get used to the technique it can be expanded to more problem behaviors. Getting started with time-out should occur after caregivers agree on this as a form of mild punishment. It should then be explained to the child before it is initially used so the child can understand what to expect the first time it is used. The child should immediately be placed in a very boring and safe predetermined location using up to ten words in less than ten seconds from the time the target behavior occurred. The child should be placed in time-out for one minute for every year of life (for example a five year old would sit in time out for five minutes) up to a maximum of about 10 minutes. A small portable timer should always be used to remind the child when the time-out is over. Once the timer rings the child will be asked why they went to time-out. Once they produce the answer the parent drops the issue and goes about their daily activities as usual. Time-out is not designed to make a child feel bad or humiliated.

Scolding is a common form of mild punishment used by parents. When scolding a child for bad behavior it is important to move close to the child, maintaining good eye contact, being stern, and expressing your feelings while naming the undesirable behavior. It is important to be brief and calm, showing disapproval for the behavior not the child. Another type of mild punishment is natural consequences. This is an event that would naturally occur after a child does a bad behavior. Some examples include not wearing an appropriate outfit to school and getting sent to the principal's office or being careless in not packing a lunch and being hungry at lunchtime. Logical consequences occur for behaviors that do not have natural consequences. Some examples include not eating all of your dinner and then not having any dessert; or riding the bicycle in the street and having the bike taken away for three days (1).

There are several ways in which parents can accidentally increase bad behaviors or decrease good behaviors. Once parents become aware of these common mistakes, avoiding them will be easier and promote a healthier parenting style. These errors include failing to reward good behavior, accidentally punishing good behavior, accidentally rewarding bad behavior and failing to punish bad behavior. A parent can fail to reward good behavior by not praising or recognizing that their child cleaned their room or brought home a great report card. Parents accidentally punish good behaviors by not being satisfied with a job well done and commenting that they could have done more or better. Some parents accidentally reward bad behavior by giving in to child who is whining and making unreasonable demands. Finally, parents can fail to punish bad behavior by ignoring it and saying something like "Oh well, boys will be boys" (1).

Common behavioral problems are challenges that all parents and caregivers face. Some caregivers have more difficulty than others in managing their children. Parents will often come to the pediatrician with questions about behavioral problems. It is important to listen to these parents, take them seriously and offer suggestions as to how some of these problems can be remedied. It is essential to praise the parents for the things that they are doing correctly and gently try to shape some of the less helpful things that they are doing in a positive way. Most children will show great improvements if the strategies in this chapter are followed. For those children with more serious behavioral problems, these strategies may not be enough and this is when the pediatrician may consider referral to a psychiatrist, psychologist or other behaviorally astute professional.

Questions

1. Which statement about solving child behavioral problems is FALSE:
    a. Toddlers and preschoolers often lack the self-control necessary to express anger and other unpleasant emotions peacefully.
    b. Children learn a lot through their parents' modeling of behaviors.
    c. Most children want to please their parents.
    d. Discipline is analogous to punishment.
    e. It takes many years for most children to be able to achieve self-control.

2. What is a TRUE statement about time outs?
    a. A good time out is when the parent praises the child outside of the child's playgroup.
    b. A terrific place to have a time out is the child's room.
    c. This method should be considered with certain types of behaviors including impulsive, aggressive, hostile and emotional behaviors.
    d. Time-out works to get a child to begin doing a behavior.
    e. A good rule of thumb is to use five minutes of time out per year of age (for example 25 minutes for a five year old).

3. Which of the following has as an example, not eating all of your dinner and then not having any dessert?
    a. Time-out.
    b. Triggering.
    c. Scolding.
    d. Natural consequences.
    e. Logical consequences.

4. Which of the following is an error in parent behavior when disciplining a child?
    a. Failing to reward good behavior.
    b. Accidentally punishing good behavior.
    c. Accidentally rewarding bad behavior.
    d. Failing to punish bad behavior.
    e. All are errors to avoid.

5. How could Sue's parent (case example) have better handled each error that they made?

6. Name three important child-rearing rules.

7. How does a parent successfully use time out? Name all the important steps?

8. What is the role of the pediatrician in helping parents with common behavioral problems?

9. When should a pediatrician refer a patient for more specialized evaluation of behavioral problems?

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Answers to questions

1.d, 2.c, 3.e, 4.e

5. Sue's parents could have used time-out to manage her bad behaviors. Since Sue is five she would have been placed in time-out for five minutes (one minute for each year of life). Spanking is chosen as a method of punishment by some parents and if this is the case it should only be one time on the buttocks and not intended to cause excess pain or injury. Parents should discuss their discipline styles behind closed doors and provide a united front with their children.

6. Reward good behavior and do it quickly and often. Avoid accidentally rewarding bad behavior. Punish some bad behavior by using mild punishment.

7. Time-out can be used initially with one or two targeted behaviors and once the parent and child get used to the technique, it can be expanded to more problem behaviors. Getting started with time-out should occur after caregivers agree on this as a form of mild punishment. It should then be explained to the child before it is initially used so the child can understand what to expect the first time it is used. The child should immediately be placed in a very boring and safe predetermined location using up to ten words in less than ten seconds from the time the target behavior occurred. The child should be placed in time-out for one minute for every year of life (for example a five year old would sit in time out for five minutes) up to a maximum of about 10 minutes. A small portable timer should always be used to remind the child when the time-out is over. Once the timer rings the child will be asked why they went to time-out. Once they produce the answer, the parent drops the issue and goes about their daily activities as usual. Time-out is not designed to make a child feel bad or humiliated.

8. Pediatricians should be available to offer counseling on routine visits with their patients. When the pediatrician observes bad behaviors in the office they should observe how the parent handles them and offer advice in a nonjudgmental way if they note errors. Pediatricians may also provide tips on effective parenting when the child is very young and be particularly sensitive to the needs of first time parents who may not know the correct way to discipline. One good way to find out how a parent is likely to discipline, is to ask them how they were disciplined as a child and the pediatrician can adjust their advice accordingly. It is very important to remain nonjudgmental and calm as you describe these techniques, as you don't want to add additional stress to a parent who is already taking on a very difficult task of raising a child. Be compassionate, listen and gently advise.

9. A pediatrician would likely want to advise a parent to see a specialist like a child psychiatrist or child psychologist if the problem seems to be more then they can handle. Some of these behaviors include extreme aggression and violence or if the child is engaging in dangerous behaviors. If the child is threatening or tying to hurt or kill themselves or others, this needs to be taken very seriously. The pediatrician will need to clinically assess the situation and decide if an emergency room visit is warranted. Threats of self-harm or harm to others should always be considered as a potential emergency.

Chapter I.8. Disabilities and Physician Interactions with Schools
Jeffrey K. Okamoto MD

Case 1. A six year old girl named Zoe with a history of prematurity and spastic diplegia comes to the outpatient clinic for an annual review. She has no new acute medical symptoms. Zoe also sees an orthopedic surgeon and a physical therapist because of the spastic diplegia. She ambulates with ankle-foot orthoses (braces) and does not require a wheelchair. She requires help when using stairs.

Her mother relates that Zoe is happy in school but does not participate in art class. This art class is on the second floor of one of the school buildings which does not have an elevator. There are no school personnel to help Zoe get to the second floor classroom. Therefore Zoe has an extra reading period instead of art since she needs continued help with reading (where she is in special education). Zoe is in regular education placement for all of her classes except for a resource classroom placement for reading. She is therefore in the resource classroom two periods everyday. Her mother wishes that Zoe could participate in art as do all of Zoe's classmates.

On exam Zoe is a happy child without outstanding findings except for hyperreflexia of her knee deep tendon reflexes, and the ankle foot orthoses that she wears bilaterally. Her ankles can be positioned past neutral passively. She enjoys drawing pictures of her family in the clinic.

Case 2. Larry, a four year old child is diagnosed with Prader Willi Syndrome confirmed on genetic testing after presenting with hyperphagia, developmental delays and pneumonia. Larry was previously evaluated for hypotonia as an infant, without any etiology being found. Larry is referred for special education services but his family finds that the school wants to wait until Kindergarten next year to place him into regular education to determine if he can do well in that setting.

Medical and school personnel have similar interests and goals. Physicians and other health personnel are focused on child health. Teachers and other school personnel are focused on child education. Therefore, both fields are child focused with interaction with families. Both want to optimize the child's potential and try to minimize problems by addressing minor problems early, before they worsen.

Both physicians and educators also deal with many mildly to severely affected children. Some children have both medical and educational issues such as Zoe illustrated above. She has cerebral palsy, but also a learning disability in reading. Some problems overlap the medical and the educational worlds. A good example is Attention Deficit Hyperactivity Disorder. Children with this condition have major impact on their school behavior and performance. They also require medical attention because of diagnostic and treatment needs. Others examples with medical/educational overlap include mental retardation, autism, blindness, and deafness. A child such as Larry with Prader Willi Syndrome has overlapping medical and educational issues.

Advances in medical care mean that more children are surviving with disabilities and medical issues. Most of these children do not need to be isolated in the hospital or in a home environment. Rather, they can do well in school environments with the proper supports. Even children with complex technological needs, such as children with gastrostomy tubes, tracheostomy tubes or ventilators, can be in school with appropriate staff and education of those in the school.

However, schools do not always understand the medical needs and supports for children with disabilities. Physicians and other medical personnel do not always acknowledge the school's perspective and difficulties in adapting to children with special needs. Physicians and schools need to collaborate as a team around these children.

There are multiple possible roles for the physician in working with schools around children with disabilities. An important role is identifying children with disabilities so that appropriate medical care, and then appropriate educational programming, can take place. A child with mental retardation or autism that goes unrecognized often loses years of specialized teaching and support that could occur in early intervention and school systems. Screening and surveillance are important activities in order to identify children early (1). Further evaluation by medical subspecialists may also be necessary to delineate the child's condition fully.

Another important role is proper referral to early intervention programs (for children up to three years of age) or to school system resources (for children older than three) for suspected or confirmed disabilities or chronic health conditions. Several federal legislative safeguards are important for children with special health care needs in the United States. Knowledge of these help physicians and other health professionals in providing oversight over children in their care in ensuring that early intervention and school programs support children with special health needs optimally.

The Individuals with Disabilities Education Act (IDEA) supports special education and related services for children and teens with disabilities. The initial federal law was Public Law 94-142 enacted in 1975 but the most recent amendments to IDEA law was in 1997 as Public Law 105-17 (2). This most recent update restructured IDEA into four parts:

Part A - General Provisions (purposes of the laws and definitions).

Part B - Assistance for Education of All Children with Disabilities.

Part C - Infants and Toddlers with Disabilities (used to be Part H).

Part D - National Activities to Improve the Education of Children with Disabilities.

Physicians can be particularly helpful in interacting with the team at the early intervention program (Part C) or school (Part B) in providing medical and other information. This can be invaluable in helping the team determine issues and services needed. Transfer of information and records from the primary care provider and subspecialists to educators is essential in many situations. Early intervention programs produce Individualized Family Service Plans (IFSPs) and schools produce Individualized Education Plans (IEPs). These are legal documents that determine the level of special education to be provided, specific goals and objectives, and ongoing monitoring and planning. Guidance for an IEP includes that it is a FAPE (Free Appropriate Public Education) in the LRE (Least Restrictive Environment). Also, a meeting to develop an IEP must be "conducted within 30 days of a determination that the child needs special education and related services" (3).

Three other laws provide protections against discrimination of children with disabilities. Section 504 of the Rehabilitation Act of 1973, a civil rights law, is helpful for children that may or may not qualify for IDEA services but require accommodations in their school program because of health concerns. For example, a child with multiple hospitalizations for asthma or other chronic illness may have accommodations such as modified homework or class assignments, altered test dates or environmental controls. The Americans with Disabilities Act (ADA) is a wide ranging law that also affects programs for children with disabilities. The Head Start Act includes provisions for children with disabilities that are enrolled in Early Head Start or Head Start programs (4).

Physicians and other health care professionals should be the "medical home" for children with disabilities or chronic health problems. The medical home provides care that is "accessible, continuous, comprehensive, family-centered, coordinated and compassionate" (1). This is interpreted by many that the medical home should participate in IEP/IFSP development, collaborate with community resources such as schools and early intervention programs, and help support and advocate for programs that support children in early intervention and school programs (5).

Therefore in Case 1 above, medical personnel and schools should discuss options to help Zoe have art activities. There should be no discrimination against the child just because of her physical disability. Accommodations could include providing training to personnel that would help her up the stairs to the art classroom, moving the art class down to the ground level, or building an elevator in the building. When a medical home representative helps problem solve with the school, creative effective inexpensive solutions often result.

In Case 2, a medical representative on the IEP planning team can help assure that critical medical reports are shared with the school (with consent from the family). Increased knowledge by the school (which may have very few or only one child with a particular syndrome over several decades) can help initiate important special education and behavioral services. Mental retardation and excessive caloric intake leading to morbid obesity are found in children with Prader Willi (6). Special education programs and control of caloric intake at school are therefore critical considerations for the IEP. Complications of the severe obesity such as early death and decline of I.Q. that results from uncontrolled caloric consumption may be decreased with proper planning with school personnel and the family.

Questions

1. The school plan that includes educational programming that can take into account medical problems such as autism or mental retardation in an 8 year old child is called a/an:
   a. Individualized Family Support Plan (IFSP)
   b. Individualized Education Plan (IEP)
   c. Individualized Health Plan (IHP)
   d. Individualized Disability Plan (IDP)
   e. Free Appropriate Public Education (FAPE)

2. A 2 year old child with developmental delays in gross and fine motor activities can get a free program called a/an:
   a. Individualized Family Support Plan (IFSP)
   b. Individualized Education Plan (IEP)
   c. Individualized Health Plan (IHP)
   d. Individualized Disability Plan (IDP)
   e. Free Appropriate Public Education (FAPE)

3. Medical professionals have roles in helping children with disabilities EXCEPT:
   a. Diagnosing children with disabilities as early as possible.
   b. Participating in school planning for the child's educational program.
   c. Collaborating as the medical home with other related services such as rehabilitative therapists.
   d. Producing the Individualized Education Plan (IEP) for children with disabilities.
   e. Advocating for families of children with disabilities so that federally mandated timelines are met in planning an Individualized Education Plan (IEP).

4. A child with a tracheostomy:
   a. Should not go to school because school personnel are not trained to care for the tracheostomy.
   b. Should not go to school because school personnel cannot handle any emergencies as a result of the tracheostomy.
   c. Should go to school as the parents can supervise the care of the child while in school.
   d. Should go to school with accommodations from a Section 504 plan.
   e. Should go to school if not requiring a nurse during school hours.

5. True/False: Schools have medical consultants paid through the Individuals with Disabilities Education Act (IDEA).

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Answers to questions
1.b, 2.a, 3.d, 4.d, 5.False

Chapter I.9. Autism and Language Disorders

Mai Anh K. Nguyen, MD

A 3 year old male presents with a chief complaint of delayed speech. Previous physicians did not find any developmental problems. He started to babble at about 9 months of age and then learned a few words such as "Dada" and "boo" at 2 years of age. His parents have tried to stimulate his language development by reading to him, interacting with him during television watching, and teaching him to mimic others' speech. His parents became more concerned as he grew older, noting his speech was less than the other children in his play group. They try to engage him in interactive activities, but he does not seem interested. They note that he is very independent and that he is very serious. He likes to play by himself rather than talking with or singing with other children. They worry that he has no playmates or friends because of his speech delay. He has been generally healthy and has had a few ear infections.

His prenatal and past medical history are otherwise unremarkable and he has not had any serious infections or need for hospitalization.

Exam: Vital signs are normal. Height, weight, and head circumference are between the 25th and 50th percentiles. His HEENT, heart, lung, abdominal, skin and neuromuscular portions of the physical exam show no abnormalities. While you are talking with his parents, you notice that he separates from them easily and he wanders about the room. He does not seem to notice that everyone is talking about him. He finds some blocks in the corner and sits down to play with them. You call out to him, but he does not respond. He starts to sort the blocks by color into groups and lines them up. He seems content playing while you finish getting the history. After you are done, you go over to him in the corner. You sit down by him and notice that he does not seem to notice that you are there. He continues to line up the blocks (very neatly) and your attempts to interrupt him are unsuccessful. Although he seems content, you notice that he does not laugh or even smile much. You also notice that he does not look at you or check back to his parents. During the session, you notice that he does not say any words.

On developmental screening, his motor development is normal. He is delayed in his language, social, and self-help skills. Subsequent follow-ups include an audiology evaluation which shows his hearing to be normal and conducive to speech development.

It can sometimes be difficult to tell a child with autism from a child with a language disorder. This chapter is an orientation to autism and related disorders, and then language disorders.

Autism is the most well known of the Autism Spectrum Disorders (also known as Pervasive Developmental Disorders). This group includes the following conditions: Autistic Disorder (Autism), Rett's Disorder, Childhood Disintegrative Disorder, Asperger's Disorder, and Pervasive Developmental Disorder Not Otherwise Specified (PDD NOS). As a group, these disorders are characterized by disturbances in three main areas of functioning: social skills, communication, and restricted or repetitive interests/activities (1).

Autism was originally described by Leo Kanner in 1943 (2). The prevalence of autism is 2-10 cases per 10,000 people. The incidence of pervasive developmental disorder (not otherwise specified) may be as high as 1 per several hundred. The incidence of Asperger's Disorder is 9 to 90 cases per 10,000. It is more common than Autistic disorder, but children with Asperger's Disorder often aren't recognized or referred for specialty care since their verbal ability is much better. Rett's Disorder & Childhood Disintegrative Disorder are both much less common than autism (1).

Autism is associated with mental retardation with studies showing up to three-fourths scoring in the mentally retarded range. These children tend to have deficits in abstract thinking, sequencing/processing information, symbolic and verbal skills. They tend to do better with motor and perceptual-motor skills.

The ratio of males to females in autism is 4 or 5 to 1 in autism (1). Interestingly, almost all cases of Rett's Disorder occur in girls. The signs of autism and the other autism spectrum disorders include:

1) Social Disturbance: Notable for lack of eye contact, poor or absent attachments, and general lack of social interest (2).

2) Communicative Disturbance: Half of those with these disorders never gain useful communicative speech. They fail to point and fail to imitate. Those who do speak may have echolalia, perseveration, pronoun reversal, extreme literalness, monotony of tones, failure to use correct cadence and intonation, failure to develop semantics (word use), failure to develop reciprocity in dialogue, and failure to use language for social interaction. Humor is usually not understood by many of these children.

3) Behavioral Features: This is notable for particular attachments to objects. They often have stereotyped (purposeless & repetitive) movements such as hand flapping or toe walking. They enjoy spinning objects or themselves. A lack of imaginative play is typical. (1)

The characteristics of each disorder can be summarized:

Autistic Disorder (Autism): To meet DSM-IV criteria, this condition is characterized by at least two specified features of social interaction, one specified feature of communication, and one specified feature of restricted or repetitive interests/activities (required to have a total of six or more items from all three areas). Delay in at least one area of social interaction, language as social communication, or symbolic or imaginative play, must be present prior to three years of age.

Rett's Disorder: Initially there is normal development and normal head circumferences. Then, there is deceleration of head growth between 5 and 48 months, loss of purposeful hand skills and development of stereotyped behaviors between 5 and 30 months, loss of social engagement, delays in language development, and poor motor development.

Childhood Disintegrative Disorder: Similar to Rett's Disorder, there is initial normal development; in this case, for the first two years of life. Then, there occurs loss of acquired skills in at least 2 areas of the following: expressive or receptive language, social skills or adaptive behavior, bowel or bladder control, play, or motor skills. Also, impairment must be present in at least two of the three areas of social interactions, communication, or stereotyped behaviors.

Asperger's Disorder: This is characterized by impaired social interaction and stereotyped behaviors. Unlike autism, there is no clinically significant delay in language or cognitive development. Many become very interested and talented in one area. For example, they may know all the dinosaurs by name, or may be fascinated about anything relating to cars.

Pervasive Developmental Disorder, not otherwise specified (PDD NOS): This disorder has some of the characteristics of the entire group of disorders, but fails to meet full criteria for any of the other four diagnoses.

The differential diagnoses for this group of disorders include language disorders, sensory impairments, mental retardation, reactive attachment disorders, childhood schizophrenia, complex motor tics, and obsessive compulsive disorders (4).

About one third are able to achieve some level of personal and occupational independence. One to two percent are able to live independently. Important predictors of outcome are intellectual level and communicative competence. Childhood Disintegrative Disorder and Rett's Disorder have the worst prognosis. Asperger's Disorder and PDD NOS have the best prognosis as they have less severe language problems and many strengths (1).

Treatment and Management of Autism Spectrum Disorders include educational interventions to foster acquisition of basic social, communicative, and cognitive skills. Examples include Floor Time, Discrete Trial Training, and Picture Exchange Communication System. Behavioral interventions are used to increase appropriate behaviors (gestures) and decrease inappropriate ones (flapping). The use of psychopharmacology (refer to the table below) is purely symptomatic; however, many do not need medications. There is no standard medication for autistic spectrum disorders.

Education and support of the family is very important. Many families hear this diagnosis as a "life sentence" without hope. Medical and educational personnel need to educate and encourage the family to use early intervention. Also physicians need to address old ideas about these conditions being caused by parental neglect (the idea of the "refrigerator mother"). There are many support groups available to help.

Advocating for the child in working with educational systems is helpful since these children need special accommodations and class structure. Physicians need to work with schools, teachers, and help families work with the educational system as well.

Unfortunately, because these are chronic disorders currently without a cure, there are quite a few alternative therapies available for families to purchase. Many of these have not been studied systematically and families need to be made aware of the monetary cost, risks, and poor results that may result from their use.

Medication considerations for autistic spectrum disorders:

Neuroleptics - may enhance learning and improve behavioral adaptation.

Tranquilizers - may decrease activity levels, increase relatedness, and increase task involvement.

SSRI - may help with inappropriate behaviors and mood difficulties.

Stimulants - may decrease hyperactivity, but may exacerbate hyperactivity in some.

Vitamins - purported to help, as children with autism are sometimes thought to have improvement of socialization and language. However, the evidence so far is very weak. (1)

Language Disorders

Language disorders are usually first noticed in early childhood. The prevalence is about 15% of children in kindergarten. Generally, children can usually produce (on average) 2 word phrases by 24 months, 3 word phrases by 30 months, and 4 word phrases by 36 months. Almost all children should be able to articulate all vowel sounds by 3 years of age. Girls generally develop speech sounds earlier than boys (2).

The characteristics of different language disorders can be summarized as:

Stuttering: This is an impairment in speech fluency characterized by frequent repetitions or prolongation of sounds or syllables (3). Difficulty is mostly at the beginning of sentences and especially with words longer than five letters. Singing is usually spared. Stuttering usually starts between two to seven years of age (2). Recovery is usually by adolescence. About 1% of children stutter. The male:female ratio is about 3:1 (3). Left handers have a higher prevalence of stuttering. Stress and anxiety can exacerbate this (2). There generally is a familial component, a biological component (laryngeal movement), and an environmental component involved (3).

Phonological Disorder: This is an impairment in the production of developmentally expected speech sounds. Evaluation of this disorder needs to rule out problems with intelligence, hearing, or the speech apparatus. The disorder is characterized by distortions of sounds, omissions of sounds, incorrect substitutions of one sound for another, avoidance of certain sounds, or reversals or misorderings of sounds. It is usually recognized at about 4 years of age. This is the most prevalent communication problem affecting 2% of school age children and 3% of preschool children (3).

Developmental Language Disorder (Specific Language Impairment): This is diagnosed when verbal intelligence develops slower than intelligence in other cognitive domains. A thorough evaluation excludes co-morbid conditions that could cause it. Two to three percent of 3 year olds have deficits in expressive, receptive, or both areas of language. This disability may affect spoken language, writing, lip reading, manual alphabet, sign language, Braille, and verbal memory (2). There are two main categories of Developmental (Specific) Language Disorders: 1) Specific expressive language disorder, and 2) Mixed Receptive-Expressive Language Disorders. In Specific Expressive Language Disorder, children are late in talking and slow to add words to their vocabulary. They generally have trouble with syntax (sentence structure) and grammatical rules. Phonological problems frequently coexist. They may also have trouble with word retrieval and tend to use word substitutions. They show an "inflexibility" of language due to their limited repertoire of language available. This may hamper their social interactions because they are 'unable' to verbally express themselves well. Children with this disorder are generally recognized by 3 years of age. Children with Mixed Receptive-Expressive Language Disorders have impaired expressive language ability combined with impaired understanding of language. Unfortunately, they often are thought to have expressive problems only. But in actuality, they also have trouble with understanding single or multi-word utterances, concepts (time, space, relationships), and multiple meanings of words. They may also have difficulties with grammatical concepts such as tenses (past versus present) or numbers (single versus plural), syntax, or slang usages.

Selective Mutism: This is a "failure to speak in one or more environments". This disorder is more common in females and seen in <1% of the population referred to mental health settings. This usually involves not speaking at school or to adults outside of the home. It is generally more of a refusal to talk rather than an inability to talk. IQ is usually average or above average. Onset is usually between 3 and 8 years of age, generally with the start of school. Some associated characteristics are excessive shyness, social isolation, school refusal, immaturity, compulsive traits, anxiety, aggression, and depression. Generally, improvement is within months or years of treatment onset. The prognosis is worse if this occurs in children over 12 years of age. A biological component, possibly maturational, suggests that children with selective mutism may be predisposed for other difficulties such as other speech or language disorders, encopresis, or enuresis (3).

Acquired Aphasia: This is development of aphasia after language development has begun. This usually occurs after 2 years of age. Encephalopathy from bacterial infections, traumatic lesions, and stroke in the dominant hemisphere are the most common reasons. This almost always results in nonfluent speech and may also progress to loss of spontaneous speech or mutism. Unless cortical damage is

bilateral, recovery in children is more likely than in adults. However, they may retain residual language deficits that may hamper their school performance. Concurrent comprehension difficulties can happen, but occur less commonly.

Landau-Kleffner syndrome: This is a rare syndrome involving nonconvulsive status epilepticus. There are severe comprehension and recognition deficits. Oral expression is worse than written expression, but both are deficient. Nonverbal intelligence is normal. 70% have hyperactivity, impulsivity, oppositional, or other behavioral problems. Prognosis is poor even with anticonvulsant medications.

The differential diagnoses for these language disorders include: deafness or hearing loss, mental retardation, autism spectrum disorders, other psychiatric disorders, organically caused communication disorder (cleft palate, apraxia, cerebral palsy, or childhood acquired aphasia).

To make the diagnosis of a particular language disorder, a variety of language assessment tools can be used. Intelligence and cognitive testing (generally nonverbal based tests) such as the WISC (Wechsler Intelligence Scale for Children) performance subscale, Ravens Colored Progressive Matrices for Children, and the Leiter International Performance Scale, can help differentiate between mental retardation and more specific disorders. Audiology tests are essential to rule out hearing deficits (2). An important part of the evaluation is determining whether or not there is a specific speech/language disorder or it is a deficit that is part of a bigger picture (genetic syndrome, psychiatric disorder, etc.) (3).

Treatment may include individual or small group therapy with a speech/language pathologist. A child psychiatrist or child psychologist may be helpful for children with Selective Mutism. Learning of Alternative Communication Methods (AAC), such as sign language or communication boards, may be crucial for certain disorders. Educational tutoring, social skills training, and behavioral interventions such as operant conditioning, contingency management (positive and negative reinforcements), and shaping of behavior are important for many children with problems occurring secondary to the language disorder. Family education and support and close collaboration with educational systems are important roles for the physician.

Questions

1. What are the three main areas affected in children with Autistic Spectrum Disorder? (Select all that apply)
   a. Splinter skills
   b. Socialization
   c. Language
   d. Motor abilities
   e. Repetitive and restricted interests and activities

2. What differentiates Language Disorders from Autistic Spectrum Disorders? (Select all that apply)
   a. Social skills are secondarily affected.
   b. Interests are not usually restricted.
   c. There is usually no repetitive behavior.
   d. Autism doesn't affect language.
   e. Most children with language disorders are not usually mentally retarded, while the majority of children with autism are.

3. Which medical disciplines generally see children with autism? (Select all that apply)
   a. Pediatricians
   b. Child Psychologists
   c. Child Psychiatrists
   d. Neurologists
   e. Family Practitioners

4. True/False: Medications can directly treat autism.

5. Which evaluations would be important in diagnosing children thought to possibly have autism or language disorders? (Select all that apply)
   a. Audiology
   b. Intelligence/Cognitive Testing
   c. Allergy testing
   d. Behavioral assessment
   e. Physical examination

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Answers to questions

1. b, c, e
2. a, b, c, e
3. all are correct
4. False, medications are used symptomatically for particular behaviors or related affective disorder.
5. a, b, d, e

Chapter I.10. Attention Deficit/Hyperactivity Disorder
Jeffrey K. Okamoto, MD

An 8 year old named Harry is accompanied by his mother to the primary care pediatric clinic. His mother relates that Harry's school wants him on a medication because he cannot sit still. He is always bothering other children in his classroom. There are 30 other children in his class. There is another boy Joel who has similar problems and is on methylphenidate (Ritalin), and is doing much better in not bothering others. Joel is now able to concentrate on his work. Harry's mother believes that Harry is quite bright but he is not learning well in his classroom. He is about to flunk math, reading and science - although he particularly likes science. His teacher says that he is well versed in identifying animals, which is part of the curriculum for his class, and he is much better than most of his classmates in doing so. However, he cannot work in a group, which is part of the science activities, without upsetting other members. He has impulsivity in working with materials and disrupts others who are trying to stay on task. Harry relates that he feels that everyone is out to get him, and that he gets teased about the teacher's frequent admonishments over his behavior. He often has to sit in a chair separated from other children. Harry's mother relates that his behavior was like this in earlier grade levels.

He is quite impulsive at home, often breaking things such as the computer and his toys. He also has broken his right tibia after riding his bicycle off the roof. He cannot sit still at meals. His mother relates that Harry's father has similar traits of being reckless, and inattentive. She relates that Harry's father is against medication for Harry. By his mother's report, Harry's father feels that he is quite successful, even after his own behavioral troubles in school during his childhood. His parents are happily married and his mother cannot think of any major social stressors other than Harry's behavior at this time.

His past medical history is unremarkable. His developmental milestones were all on time prior to age five.

Exam: VS T 37.2, P 105, R 16, BP 90/43. Height and weight are at the 20%ile. Head circumference is near the mean for age. He is happy and active, exploring the office, touching all medical instruments. He speaks coherently and in context, seems sad and then mad when talking about school. He draws a picture of three figures when asked to draw a picture of his family doing something. They are all swimming in the ocean. By Goodenough-Harris scoring, his figures in the drawing are at a 9 year old level. He has no dysmorphic features. His head, eyes, ears, mouth, dentition and neck are normal. His heart, lungs and abdomen are normal. No facial asymmetry or tics are observed. He moves all extremities well. He walks and runs well. He has good muscle tone and strength, without contractures or tremors. His DTRs are 2+/4 for knees, ankles and biceps. He has no rash and no neurocutaneous lesions. His hearing and vision screens were found to be normal.

Harry is evaluated using a variety of methods looking into several domains of his life. Behavioral rating scales (the 1997 revision of the Conners Rating Scale) shows Harry to be above two standard deviations in Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms for both the Teacher and the Parent scales. A school psychoeducational assessment shows Harry to be above average in both performance and verbal IQs, although the examiner did relate that it was difficult to keep him focused on the tasks presented. He is at the 2nd grade level for his reading and writing, but the 3rd grade level for his math and listening comprehension achievement tests.

A behavioral management program is started at his school. He is given preferential seating and he has a rewards/consequences system for keeping on task or if bothering others. He is tried on psychostimulant medication with some loss of appetite. With titrating of the dose, he is found to be much less distracted in school, and he pays much better attention to class activities. A counselor helps Harry learn how to maintain group activities without the other children becoming mad, and gives Harry insight into following rules on the playing field. He is eventually placed in a "gifted and talented" program at his school because of the excellence of his schoolwork and achievements. Medication holidays help maintain his growth.

Attention-Deficit/Hyperactivity Disorder (ADHD) and its treatment have been controversial areas in the US. Because of the number of children thought to have this condition and the number of prescriptions written for this diagnosis, alarmed families and civic groups have wondered if this condition is overdiagnosed. They also worry that medications are overly used and that medications for this condition will be abused or lead to future drug abuse.

However, without diagnosis and treatment, these children face school failure, poor self esteem, drug abuse (ironically), and multiple other problems. The astute clinician understands family and societal concerns, the natural history of the condition, diagnostic tools, and important treatment modalities in order to prevent or ameliorate major problems.

It has been estimated that 3% to 7% of school age children have ADHD (1). Currently, ADHD is the most common neurodevelopmental disorder of childhood (2). With such numbers of children affected, pediatricians and other primary care providers have an important role in assessing and managing many of these children. There are not enough neurologists, psychiatrists, psychologists or similar subspecialists for all children thought to be affected. Boys are diagnosed at least three times as often as girls (3).

Diagnostic criteria can be found in the DSM-IV-TR version of the Diagnostic and Statistical Manual of Mental Disorders (1). Unfortunately, labels and criteria have changed over the years, causing some confusion among practitioners and research groups (4). Previous diagnostic labels have included Minimal Brain Dysfunction (MBD) and Attention Deficit Disorder (ADD). Physicians in Europe and other countries use the term Hyperkinetic Disorder (HKD).

However, it is clear that whatever term is used, this is a clinical diagnosis based on a history of symptoms in multiple environmental contexts observed over time. The core areas that need to be delineated are inattention, hyperactivity and impulsivity. DSM-IV-TR relate three subtypes: 1) a predominantly inattentive type, 2) a predominantly hyperactive-impulsive type, and 3) a combined type. DSM-IV-TR criteria also include the stipulation that some symptoms that caused impairment were present before 7 years of age. Impairment has to be in two or more settings (for instance home AND school), and there must be clear evidence of significant impairment in functioning in interrelationships, schoolwork or in job performance (1). Interestingly, if impairment in school performance and behavioral functioning are not used as part of the criteria, the ADHD prevalence is much higher - 16.1% without impairment criteria versus 6.8% with this criteria (5).

There is also a category in DSM-IV-TR for ADHD, NOS (not otherwise specified) that can be used for children and adults that do not meet criteria for the above mentioned subtypes but have significant impairment from such symptoms. Primary care providers still need to help families and schools with children who do not meet full DSM-IV-TR criteria but have characteristics that cause impairment.

Usually the diagnosis is made in the school age years. High activity levels in toddlers do not invariably lead to ADHD in childhood. Many "hyperactive and inattentive" toddlers end up focusing and engaging in activities without impulsiveness and hyperactivity after maturing through their preschool and early school years. However, one study showed about 1/2 of children thought to have ADHD in their preschool years had a clear diagnosis by age 9 years. These children had more severe symptoms in their preschool years overall compared

to peers (6). Therefore, a clinician needs to take great care to understand the ramifications of the child's age but still consider ADHD at these younger ages.

Much discussion has ensued on whether children with ADHD are just part of the normal continuum of children with varied levels of attention, activity and impulsivity. There is no firm evidence that shows a bimodal distribution where children with ADHD are clearly separate in a different part of the continuum. A recent National Institutes of Health report likens ADHD to essential hypertension or hyperlipidemia which are continuous throughout (and not bimodal) in a population, and where the importance of diagnosis and treatment has been shown (7).

The cause of ADHD is still being elucidated. Brain imaging studies (including MRI, PET and SPECT) show differences compared to healthy controls (8). There is a significant genetic inheritance component. Studies have started to implicate genes for dopamine in ADHD. This correlates with the fact that medications clinically helpful for ADHD involve dopamine transmission. Also, imaging studies have shown the frontostriatal regions of the brain to be important, which are rich in dopamine related neurons. Lastly, mice with impaired dopamine transport mechanisms, are hyperactive and resistant to medications (9).

Once diagnosed, ADHD appears to continue into the teen years for about 3/4 of the diagnosed pre-teen school aged children. Untreated, they often have more severe problems with their peers and family. Problems are worsened because of the multiple previous experiences of failing in endeavors, and also the bad relationship patterns that have been built up with family members (10). One half will have oppositional defiant disorder (ODD), conduct disorder (CD), or another psychiatric diagnosis in their teen years. Also, 1/4 will have comorbid learning disabilities (LD), which can be seen in a discrepancy between their scores in tests of learning ability as compared with achievement.

Interviewing the child and family is of utmost importance. Detailed history gathering will reveal the child's characteristics. Also the history should reveal whether the child's problem is in single vs. multiple settings, and how long symptoms have been noted over time. One needs to be careful not to use the child's appearance in the clinic visit as a measure of the child's problems. Children with (and without) ADHD often look different in structured, supervised, and/or novel settings such as a doctor's exam room. Although some children will show inattentiveness and hyperactivity in the clinic office, some children with severe ADHD may look fine in this setting (8).

Tools that can help in the diagnosis of ADHD include parent-child structured interviews which psychologists and psychiatrists are often familiar with, and ADHD behavioral rating scales which most child professionals have some familiarity with. Barkley, in his well known handbook for assessment and treatment of ADHD has detailed chapters regarding these (11). He finds that ADHD specific behavioral rating scales can be useful for a diagnostic assessment of a child or adolescent. Other reasons for using behavioral rating scales include evaluation of response to medication or child response to parent training in behavioral management. An analysis has shown the use of more global behavioral rating scales to not as effectively detect ADHD compared to ADHD specific scales (2).

After this careful information gathering, a clinician needs to decide if a particular child meets criteria for ADHD and whether an alternative diagnosis is primary. Other disorders that can affect attention include anxiety disorders, mood disorders, substance abuse, and schizophrenia. Head injury, seizure disorders, and brain infections can lead to symptoms of ADHD (8). Although hypothyroidism, fragile X syndrome, glucose-6-phosphate dehydrogenase deficiency and phenylketonuria have all been associated with ADHD, testing for these conditions have very low yields and are not suggested unless the history or physical suggests these in other ways (8). Also electroencephalograms (EEGs) and computerized Continuous Performance Tests (CPTs) have not shown sufficient consistent discrimination between children with and without ADHD (2). Children with lead toxicity as toddlers or preschoolers show normal lead levels by the time they are tested in the school age years. Therefore lead screening is also not recommended on a routine basis (2).

The conditions that are most commonly confused with ADHD are mood disorders and anxiety disorders (8). Both of these disorders are often episodic (and not continuous and unremitting like ADHD), with a later age onset compared to ADHD. Some clinicians like to treat the mood or anxiety disorder first, if one of these are suspected, and see if the symptoms of ADHD resolve.

Comorbid conditions that are often found in combination with ADHD include ODD, CD, LD, Tourette's disorder and speech/language disabilities. All of these may also be disorders that may mimic ADHD in some ways (for example a child who appears inattentive because of language processing disorders) but have substantial differences in criteria from ADHD.

Treatment of ADHD requires understanding of four aspects delineated in a recent American Academy of Pediatrics guideline (12):

1) ADHD is a chronic condition. Physicians should be working with families and schools over the long term to help support these children into adulthood. Follow-up over years is required. Initially the clinician needs to inform the family about ADHD. Then this provider will need to work with the family in coordinating other professionals as necessary, involve the family in treating the child and debriefing the situation, and connect the family to support groups as they desire.

2) Target symptoms need to be addressed. Physicians need to negotiate with the child's family and school over which target symptoms will be addressed at any particular time. These target symptoms should have the potential of being improved upon with appropriate support. These also need to be explicit and measurable. An example of a poor target would be to request the child to be a "good" child. More appropriate targets would include: a) Improvement of the relationships with people the child interacts with; b) Abating behaviors that interfere with the activities of others; c) Working on schoolwork being completed with improved accuracy and decreasing the time necessary for completion; d) Being able to work without supervision in schoolwork, homework and activities of daily living; e) Having better self esteem; and f) Improving safety skills.

3) Medication and behavior strategies are important. Many parents want to use only behavioral strategies rather than medication. Interestingly, the American Academy of Pediatrics' review that examined different treatments of ADHD rated medication as "good" and behavioral strategies as "fair" in strength of evidence. This was particularly affected by the Multimodal Treatment of children with ADHD (MTA) study (13). This study randomized 579 children with ADHD from ages 7 to almost 10 years of age to different groups: medication management alone, medication and behavior management, behavior management alone, and a standard community care group. Both groups that involved medication showed a substantial decrease in important ADHD symptoms over a 14 month period. The combined treatment group showed improved academic measures, measures of conduct, and some specific ADHD symptoms (although not on global ADHD symptom scales) compared to the single treatment groups. In reviewing most of the studies comparing behavior therapy with stimulants alone, there seems to be a much stronger effect from stimulants than with behavior therapy (9).

Medications used in ADHD include stimulants such as methylphenidate and dextroamphetamine; antidepressants such as imipramine and desipramine; and alpha-adrenergics such as clonidine. One of the stimulants, pemoline, was more widely used in the past but this has been advised against because of toxic hepatitis and acute hepatic failure (about 4 to 17 times the expected rate). Monitoring liver function tests usually does not alert the practitioner quickly enough to prevent the rapid progression of liver failure. The other more widely used stimulants have no such liver toxicity. Methylphenidate and dextroamphetamine have side effects such as appetite suppression (about 80%) and insomnia. Overall either of these two medications may cause short term slowing of weight gain and growth

but long term effects are minimal. Tics may be precipitated in those predisposed to them, with improvement often seen while on drug holidays (9). A new non-stimulant medication, atomoxetine (Strattera) is now an available treatment option.

Stimulant medications show quick and often dramatic results in the ADHD characteristics of children. Unfortunately children without ADHD have similar behavioral responses so the response from medication should not be used as a diagnostic trial. Interestingly, good behavioral effects have been repeatedly shown but long term academic effects have not been shown in any long term trial yet. Antidepressants have also shown good initial efficacy but not sustained effects compared to stimulants. These medications are usually reserved for those with coexisting disorders (such as depression and tics) since they have a higher risk of sudden death which cannot be predicted with plasma drug levels or electrocardiography. Clonidine has also led to sudden death when used in combination with methylphenidate. This medication has a patch form that some families prefer. Serotonin-reuptake inhibitors have no evidence based effects that have been shown (9). Newer delivery systems for more sustained release of stimulant medication (such as Concerta, a time released form of methylphenidate) show great promise. They enable a dose prior to school that lasts 12 to 14 hours, rather than requiring the child to go to the school nurse to obtain another dose after the 4 to 5 hour duration of a short acting stimulant (14).

Behavioral Strategies for children with ADHD include: a) Positive reinforcement (providing desired reinforcers contingent on the child's behavior and activity); b) Time-out (using ignoring and isolation away from desired activity); c) Response cost (taking away rewards or privileges if undesired activity takes place); and d) Token economy (a form of positive reinforcement where the child obtains "tokens" such as stars that can be collected towards a even more strongly desired reward) (12).

4) Close follow-up of target symptoms and medication use. Reevaluation of whether the child has ADHD, a comorbid diagnosis, or another diagnosis altogether is important. Target symptoms should be measured by multiple methods if possible and treatment modified as necessary. These reevaluations and monitoring should be done periodically and consistently. The frequency of follow-up would depend of the severity of ADHD, other important comorbid conditions or factors, and the effects and complications of treatment.

In the past it was thought that most children with ADHD would have most of these symptoms abate when they become adults (after a rocky adolescence as mentioned above). It is known that many still have the characteristics for the criteria of ADHD in adulthood, and many have significant problems in work, school or other environments (3). Because of the genetic predisposition, many of the parents of the children seen for ADHD will also have ADHD. This complicates management since parents are essential for the child with ADHD to administer medication, and to ensure behavioral follow-through and academic planning.

Questions

1. True/False: A child psychiatrist is necessary to diagnose and manage children with ADHD

2. The different subtypes of ADHD in DSM-IV-TR relate to criteria around (select all that apply:)
    a. Inattention
    b. Particular learning disability
    c. Impulsivity
    d. Hyperactivity
    e. Gender

3. Evidence is accumulating that shows ADHD to be connected to (select one):
    a. Serotonin
    b. Mast cells
    c. Cortical sleep centers
    d. Dopamine
    e. Mental retardation

4. Which is the LEAST important concern in managing children with ADHD? (select one):
    a. Parents of children with ADHD may have ADHD themselves.
    b. Target symptoms need to be addressed.
    c. The teen years.
    d. Side effects from Pemoline use.
    e. Growth problems from psychostimulant use.

5. Which should be used routinely in the evaluation of school aged children with ADHD? (select one):
    a. Lead screening.
    b. Electroencephalograms (EEGs).
    c. ADHD specific behavioral rating scales.
    d. Fragile X chromosomal testing.
    e. Parent depression inventory.

6. Which is a common comorbid condition with ADHD?
    a. Learning Disability
    b. Autism
    c. Obsessive Compulsive Disorder
    d. Diarrhea
    e. Seizure disorder

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Answers to questions
1. False, 2.a,c,d, 3.d, 4.e, 5.c, 6.a

Chapter I.11. Medical Insurance Basics
Richard Y. Mitsunaga, MD

You have just completed an examination on a two-year-old child. The child seems normal in nearly every respect, but has only ten words in her vocabulary. You refer her for a speech and hearing evaluation. A developmental expressive speech delay is diagnosed. Speech therapy is recommended. The insurer declines to pay for this service because treatment of developmental language disorders is not a covered service in the patient's health plan.

Our professional survival depends on providing quality services for the patient at a fair cost and receiving just compensation for these services. Accordingly, a basic understanding of how things are paid or not paid is essential. This is particularly true when advocating for patients and for fair reimbursement.

Numerous terms and acronyms confront the newcomer to the field. The terminology must be learned, just as the anatomical, chemical and physiological terms, which were so foreign to you a few years ago, had to be learned. Salaried physicians who do not have formal fiscal duties must still understand the insurance systems used by their patients or risk making them spend more than they should under terms of their coverage. This can cause patient dissatisfaction despite excellent health care and results. It can cause medical-legal problems if the patient's outcome is less than optimal.

A glossary of the more common terms used herein is located at the end of this chapter to assist you with this new terminology. A more complete glossary is contained in other works (1). Some of the definitions used in this chapter are taken from that reference. Every contract you sign with an insurer contains definitions of the terms used in that contract. You are advised to read these carefully so you understand what you are agreeing to do.

A third party payer is an insurer; an entity contracted to arrange payments for services rendered to a patient. The payer may be an insurance company, mutual benefit society, a self-insured large employer, or a state or federal agency.

It is important to understand that an insurer pays with the patient's money, not its own funds. Money from premiums is redistributed as payments. This helps to protect patients from unexpectedly high expenses because the risks are spread among many subscribers. At the same time, it imposes an obligation on all parties to use the money wisely, just as if the payment was coming directly from your patient's pocket.

Sixty years ago, there were few insurers dealing with health. Physician's and hospital fees were paid from the patient's personal funds. Many did not seek medical care because they couldn't afford it. Physicians wondered with every decision whether or not the patient could afford the cost of their recommendations. By the 1960s, there were more health insurance plans. Most dealt with inpatient care, but outpatient plans were rapidly developing. Hawaii pioneered mandatory employer coverage by enacting the nation's first prepaid health care act in 1974. Hawaii's law requires covering only the employee, but charges for a family plan were then low enough that many employers incorporated them into their company plans. Medical costs were inexpensive by current standards. Hospital charges for a five-day mother-baby stay (average at the time for a normal vaginal delivery) in the mid-1960s were about $350, which included the delivery room.

There are four basic components to the American health care system. First are the patients who need care. Second, there are the professionals who provide care, including physicians. Third are the various institutional providers, including hospitals, that also provide care. Finally, there are those that pay for the services rendered by the providers. This may be the individual with or without a third party that assists in payment. These include private as well as government insurers such as Medicare and Medicaid. All parts are essential. In this era of high cost treatment and technology, the system collapses if one piece is missing. The focal point must be the patient. There is no reason for the existence of the others if no one needed their services.

HOW DO PHYSICIANS GET PAID? The person who owes the funds for professional services is the patient. Today, very few patients (or their families) are wealthy enough to pay for all their medical needs. As in the past, patients who have no outside financial assistance must compromise on the visits they make and the treatments they receive. This is far from ideal.

Usually, physicians are paid via some intermediary, which can take many and varied forms. All share a basic cash-flow pattern in which a service is rendered and a charge is made. A payment is then received. A physician must pay business expenses ("overhead"), including working space, personnel including professional (e.g., office nurse), clerical and maintenance, supplies, taxes, malpractice insurance, etc. Only afterward does the physician get paid. In an average pediatric office, overhead runs between 45 and 60 per cent of the gross revenues. If the physician does not attend to the business aspects of the practice, someone must be paid to do this. This administrator adds to the overhead expenses of the practice.

Physicians may be in solo or group practice. Groups may be as few as two physicians or there may be hundreds. Groups may consist of a single specialty or be a multispecialty group.

Payments to the physicians can take varied forms as well. In its simplest form, a practitioner keeps what is left after expenses and taxes are paid. More commonly, a fixed amount is taken and the remainder saved as a reserve. Physicians in groups may organize in an office-sharing arrangement, partnership, professional corporation or partnerships of individuals and corporations. Individuals may incorporate as well, by creating a legal entity known as Dr. XYZ, Incorporated. Payments may occur by taking a fixed amount from partnership revenues (called a "draw") each month, by salary, or by various formulas used to measure productivity and other contributions to the group such as administrative duties. There are also physicians who are employed by large entities such as a university, hospital, health care groups (e.g., Straub, Kaiser Permanente), federal or state agency or department, including the Military Services and the Public Health Service.

HOW DO INSURERS GET PAID? Insurance plans are basically capitated, which means that they receive a fixed amount per patient with which care must be provided for the contractual period, e.g., one year. This is true of private payers as well as government sponsored plans. Military services have congressional appropriations. How they distribute the funds to individual providers, hospitals, pharmacies, etc., is determined by each plan. This accounts for the multitude of payment billing and reimbursement methods encountered by physicians.

The funds received by an insurer represent the amount a purchaser (individual, employer, government agency, etc.) is willing to pay for the total services. The insurer must negotiate for a payment rate within which it can function and remain solvent. The insurer cannot create more money, so it is responsible to distribute the monies it receives fairly but wisely. Bankruptcy of a health plan is catastrophic, as its patients are left without health insurance and money owed to providers cannot be paid. Sufficient reserves must be maintained to provide for unforeseen variations in usage as well as emergencies so that patients and providers are protected.

Repeated withdrawals from reserves can rapidly deplete them, so insurers must operate within their budgets. This is limited to the amounts employers or individuals who buy the policies are willing to pay for premiums minus the operating expenses of the insuring company.

In the days when health insurance was scant or non-existent, physicians sent their patients a bill "for services rendered" and expected to be paid. It is more complicated now, but the fundamentals are the same. Currently, most patients have a large part of their medical expenses paid by a third party payer, who expects a more detailed statement of what services were rendered. How do patients and insurers know what services were delivered and what must be paid for? Most insurers use a standard claim form, called the HCFA 1500 form, to receive reports from providers on the services rendered, diagnoses and the fee requested. Knowledge of what goes on this form is essential even for salaried physicians, since large employers of doctors frequently use these forms as a measure of a physician's productivity and the complexity of the patients who are seen.

Most providers use a computerized billing program. This saves time with the collection of standardized information on a HCFA 1500 such as the patient's name, insurance number, etc. Additionally, computer billing permits better record keeping than is conveniently possible with a manual system, particularly when data retrieval or summaries must be prepared.

From your medical notes, ICD codes (see glossary) convey the diagnoses the patient has and CPT codes tell what level of service(s) was done, along with your charge for those services. Basically, these systems are intended to provide a quick way of informing the insurer about what was done.

Unfortunately, there is opportunity for exaggeration or gamesmanship by provider or insurer. Providers may exaggerate the level of the services provided or they might "unbundle" charges, which refers to charging separately for services that are normally provided as a package. Insurers may be arbitrary in "downcoding" claims, which refers to adjusting a provider's claim to a lower paying level or by refusing to recognize "modifiers" which are codes reflecting unusual complexity of the services rendered.

Both sides may retain coding experts, whose job is to extract the most benefit for their side, often using whatever technicalities they can muster. The codes are supposed to be a method of communication, but this often gets lost in the exchange. Codes were neither intended to give providers an opportunity to game insurers nor to provide insurers with a method to cheat providers. Until mutual trust and meaningful communication is established, part of the monies that could be spent for paying claims will be diverted to review activities. State law and provider contracts with insurers provide for appeals and one should be filed if it is felt that a patient's claim or your bill was unfairly denied. Appeals without merit, however, also cost the insurer money to review and process, and this is money that might be better spent paying claims.

It is critical to know that insurers including the government require adequate documentation of a service. For review purposes, a service not documented is considered to have never been performed (and will not be paid for). In short, documentation of the services rendered and a thorough knowledge of coding rules and procedures are essential to receiving the best compensation for your services. Coding is best done by the physician. It is a mistake to assign this duty to less experienced helpers.

Provider contracts with third party payers include provisions for fee schedules to be established. You may charge whatever you wish for a given service, but the insurer will pay no more than the "maximum allowable charge" (the amount for a service listed on the fee schedule) for the service. The difference between your charge and the lesser amount allowed is called a "provider adjustment," which is a discount off your fee that you have contractually agreed to with the insurer. Patients receive a report of this "provider adjustment" and all

insurers stipulate you cannot "balance bill" (i.e., charge the patient for the difference between your charge and the maximum allowable charge). If your fee is less than the maximum allowable charge, you will be paid only what you charged.

For a given claim, an insurance company pays a contractually agreed percentage of the allowable charge. For example, it may pay 80% of an office visit (the actual percentage varies with different plans). The patient must pay the "co-payment" which is the balance owed between the allowable charge and the amount paid by the insurance company. In this case, the patient will owe 20% of the bill plus applicable state tax. You bill the patient for this "co-pay". This is the typical fee for service (FFS) arrangement. One could consider "capitation" to be the opposite of FFS. Physicians who are capitated will receive a monthly payment for each patient registered to them by that insurer regardless of the number of visits that month.

Variations in the system are common. A large group or an IPA (Independent Practice Association) may receive a capitated payment for the patients under their care. This intermediary may choose capitation or a fee for service method of paying the physicians who render the care. Be sure you have a good explanation of the payment mechanisms that apply to you.

Obligations to patients by providers and by third party payers overlap, but not completely. Both providers and insurers are expected to provide those medically necessary services authorized by the terms of the physician's contract and the patient's coverage.

It is important to know that an insurance policy rarely covers all possibilities, but rather only those services that are "covered services" and are "medically necessary" (a term that is defined in state law) will be paid for. If a service is not covered in the patient's plan, it won't be paid for even if it is "medically necessary". An analogy exists with auto insurance. You won't be paid to fix your wrecked car if you didn't buy collision insurance or if you wrecked the car doing something excluded by your policy such as driving without a license. The sample case at the beginning of the chapter is another example, such that developmental speech abnormalities were not a covered service in the patient's plan, even though the need for the service is appropriate. Other services must meet specific criteria and be "pre-authorized" by the insurance company (i.e., be approved for coverage in advance or risk not having it paid for at all).

Providers are obligated to provide individualized services to each patient. Some community obligations exist, such as not abusing antibiotics and causing the development of resistant organisms, but the basic obligation is to the individual patient. Third party payers must consider their total membership and the community as well as the individual member. Prices must be affordable for those paying the premium and insurers have an obligation to remain fiscally solvent through the terms of their contracts. Accordingly, covered tests and treatments must be of proven efficacy and cost-effectiveness. Adequate reserves must exist to protect against unforeseen events. The differences in these obligations can lead to occasional conflicts.

There are fewer conflicts than people on both sides think. The overwhelming majority of claims are paid promptly and automatically. Neither side pays much attention to them because they are not a problem. Providers and payers interface when a conflict occurs (e.g., a denial of a prior-authorization request or a payment). Attention is paid only to the conflicts and both sides often have a very limited view of the other's role and the fact that their obligations may differ. An insurance company's staff that works all day with denials may incorrectly feel every physician is trying to cheat. The provider, whose attention is called to denials and not to the majority of claims that are immediately paid, may feel that all the insurer does is try to cheat them. The perceived frequency of these conflicts is therefore magnified.

Reason must prevail and discussions must change from the "win-lose" mentality currently prevalent. Conflict resolution must occur with each side appreciating the other's role in the overall scheme of managing patient care. Above all, communication is essential. Even agreeing to disagree on a given point is better than not communicating at all.

Questions

1. True/False: The decision to deny speech therapy in the case at the beginning of the chapter should be appealed, since it is medically necessary.
2. True/False: A cosmetic procedure is denied because it is not a covered service. The patient elects to have the procedure anyway. The doctor is allowed to charge for the service.
3. True/False: A charge is adjusted downward because it exceeds the maximum allowed for that service. The doctor is allowed to charge the patient for the difference.
4. True/False: A mechanism to appeal managed care decisions is contained in Hawaii State Law.
5. True/False: Due to their large reserves, insurers have minimal budgetary constraints in spending.

References

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Answers to questions

1. False. The service is not covered in this patient's plan even if it is deemed medically necessary.
2. True. The patient must be informed beforehand that the service may not be covered and that he or she will be expected to pay if they wish to have the service done.
3. False. Contracts between third party payers and providers stipulate that balance billing is not allowed when fees exceed maximum allowable charge on a covered service.
4. True. See Hawaii Revised Statutes Chapter 432e.
5. False. An insurer must observe its operating budget, which is dependent on the premiums received. Insurers cannot generate new money; they can only redistribute what they collect after expending reasonable amounts for operations. Reserves are for unforeseen emergencies. Repeated withdrawals from reserves threaten the solvency of the third party payer.

Glossary (1)

Capitation: A method of payment in which reimbursement to a provider or group of providers occurs through the payment of a fixed, periodic payment (usually monthly) in exchange for delivering a defined set of services to a specific population of patients, placing most of the financial risk for utilization on the provider. This is paid whether a patient has no visits or makes multiple visits (1).

CMS (Centers for Medicare and Medicaid Services): Formerly HCFA (pronounced hik-fa for short) or Health Care Financing Administration. This is the federal agency responsible for administering the Medicare, Medicaid, SCHIP (State Children's Health Insurance), HIPPA (Health Insurance Portability and Accountability Act), CLIA (Clinical Laboratory Improvement Amendments), and

several other health-related programs. Additional information regarding CMS and its programs is available at http://cms.hhs.gov/about/default.asp.

Cost Effective Care: Defined in Hawaii Law (Hawaii Revised Statutes Chapter 432e) as "a health intervention where the benefits and harms relative to the costs represent an economically efficient use of resources for patients with the medical condition being treated through the health intervention; provided that the characteristics of the individual patient shall be determinative when applying this criterion to an individual case." "Cost effective does not necessarily mean the lowest price."

Covered Services: Those services contractually or legally required of a third party payer. In Hawaii, the latter includes childhood preventive health services and immunizations through age five years.

CPT: Current Procedural Terminology. Developed by the American Medical Association, CPT is revised annually and is a listing of descriptive terms and identifying codes for reporting medical services and procedures performed by physicians.

Downcoding: The practice of designating a lower level or intensity of medical service provided for purposes of paying less to health care providers (physicians, hospitals, etc.). Downcoding is correct if the documentation does not reflect the service claimed. Insurer's can abuse downcoding if it is done arbitrarily or solely to pay the provider less.

EPSDT: Early Periodic Screening Detection and Treatment. A program on which the QUEST (Hawaii Medicaid Managed Care Program) Plans are rooted. All patients under age 21 years are considered to be in EPSDT, which makes them eligible for some benefits that are not available to adults.

FFS (Fee for Service): A mode of payment for health care services in which a physician charges a fee for each specific service or group of services. The patient and their insurer pay, usually in a ratio of 20% from the patient and 80% from the insurer. Plans covering FFS arrangements are typically the most expensive.

Formulary: A list of approved prescription drugs determined by a managed care plan for use by its patients and physicians (1).

HMO (Health Maintenance Organization): An entity that agrees to provide or arrange for the provision of a specified set of comprehensive health services to a defined population of patients for a prepaid, fixed sum (1).

ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification). A system of disease classification based on work by the World Health Organization and issued in the United States by the U.S. Department of Health and Human Services. The CM version refers to the standard method physicians use to report their diagnoses on an individual patient to insurers on their claims for payment.

IPA (Independent Practice Association): An association of physicians organized to provide various services for their members, including securing contracts with insurers, particularly for managed care contracts. IPAs may also do MSO functions (see MSO).

Managed Care: A means of providing health care services within a defined network of health care providers that is given the responsibility of managing utilization of health care services and providing quality, cost-effective health care (1).

Medicaid: A jointly funded, Federal-State health insurance program for certain low-income and needy people. It covers approximately 36 million individuals including children, the aged, blind, and/or disabled, and people who are eligible to receive federally assisted income maintenance payments (see QUEST).

Medicare: Health insurance program administered by the Centers for Medicare and Medicaid Services (CMS) for persons 65 years of age or older, some persons with disabilities, and patients with End-Stage Renal Disease. Medicare has two parts: Medicare Part A (hospital insurance) helps pay for care in hospitals, skilled nursing facilities, hospice care and some home health care. Medicare Part B is optional for beneficiaries and a premium must be paid. Part B helps pay for doctor's services, outpatient hospital care and some other medical services that Part A does not cover.

Medical necessity: To a physician, this has classically meant whatever a physician deems necessary in the care and treatment of an individual patient. Patients, of course, define the term as referring to services they feel they need. Third party payers changed this to refer to care that their payment teams deemed necessary for the management of a given patient. The term has become increasingly complex and specific criteria must be met for a service to qualify as "medically necessary". Hawaii has a definition of Medical Necessity defined in State Law.

MSO (Management Services Organization): An entity that provides management services to physicians, physician groups, hospitals or insurers. Services may include quality and utilization management and claims payment. An MSO can be owned by any of the entities for which it provides services, various combinations of the owning entities, or be completely independent (1).

PPO (Preferred Provider Organization): Groups of physicians usually assembled by an insurer or other large entity to provide services for its membership. Physicians in such a group are usually contractually required to participate with the plan, which generally includes items such as accepting payments that are reduced from the full payment usually given by that insurer. In return, the insurer guides its subscribers to utilize the preferred providers. Other contractual requirements may include mandatory participation in aspects of the plan to monitor quality or to save money, such as following a formulary.

QUEST: Medicaid Managed Care Program administered by the Hawaii State Department of Human Services.

Upcoding: The practice of designating a higher level or intensity of medical service provided for purposes of obtaining greater reimbursement from an insurer or other payer (1). Upcoding is appropriate if a higher level of service was actually rendered; inappropriate if it was not.

Chapter I.12. Pediatric Dental Basics
Cindy W. Yang

A 2 year old boy is brought to the office by his mother, who is concerned that her child has not been eating normally and has many dark spots on his teeth. He might be having dental pain, but she is not sure. Acetaminophen has been given, and this might be helping to some degree. His mother reports trying to wean him off the bottle. She typically feeds him at night, and he refuses to go to sleep without a bottle of milk or apple juice. She doesn't brush his teeth because he doesn't like it. She has never taken him to a dentist due to financial reasons. His past medical history and family history are unremarkable.

Exam: VS T 37.5, P 85, R 25, BP 95/55. Height and weight are at the 75th percentile. He appears alert and active in no apparent distress. His physical exam is normal, except for findings in the oral cavity. Intraorally, there are opaque brown and grey specks on the enamel surface of several upper primary teeth. The upper central and lateral incisors show extensive decay and are slightly loose. The gingival tissues above the upper right central incisor are slightly swollen. Moderate lesions are visible in the upper canines, upper first molars, and lower first molars. The upper and lower second molars are just emerging through the gingiva. The lower canines and incisors are all intact, with no signs of dental decay.

A diagnosis of early childhood caries (ECC) is made, and he is referred to a dentist. His mother is told to wean him off the bottle and to brush his teeth at least twice a day.

Pediatricians and primary care family physicians play a vital role in promoting good oral hygiene as a life long habit that begins during infancy. They are the first and most frequent health care providers seen by infants and young children, during the formative years of oral health care. Beginning from the newborn period, they are also the first to provide information and guidance to infants and their parents. The key to oral health promotion and disease prevention lies in anticipatory guidance and education of parents, early detection, and timely referral for appropriate intervention.

A general knowledge of basic dental anatomy and tooth eruption patterns enables the primary care physician to evaluate a child's general oral health. The primary structures of the tooth are the: 1) enamel (outermost protective layer), 2) dentin (calcified tissue layer deep to the enamel), 3) gingival margin (region of the gum surrounding the tooth), 4) pulp (soft tissue at the core of the tooth which contains blood vessels, nerves and lymphatics), 5) cementum (layer of bony tissue covering the tooth root surface), 6) periodontal ligament (membrane around tooth attaching it to alveolar bone), 7) alveolar bone (bone that surrounds the root and forms the socket for the tooth), 8) neurovascular bundle (nerves, arteries, and veins in the dental pulp that exits at the root of the tooth).

Teeth can be named by their anatomic shape or by a letter/number convention used by dentists to describe the upper/lower and left/right teeth. Letters refer to primary teeth and numbers refer to permanent teeth. There are 20 primary teeth (described by positions A through E) and 32 permanent teeth (described by positions 1 through 8). From the center proceeding posteriorly: central incisor (#A, #1), lateral incisor (#B, #2), canine (#C, #3), first premolar (#4), second premolar (#5), first molar (#D, #6), second molar (#E, #7), third molar (#8).

The formation of human dentition begins as early as the 6th week in utero, during which, tooth buds of the primary (deciduous) teeth develop at 10 specific sites in the developing maxilla and mandible (1,2). Primary teeth begin to calcify at about 3 to 4 months in utero, and the enamel of all crowns is completed by 10 months after birth. From the midline of the oral cavity, anteriorly to posteriorly, the primary central incisors are the first to erupt at about age 6 to 7 months, followed by the lateral incisors at 7 to 9 months, the first molars at 12 to 14 months, the canines at 16 to 18 months, and the second molars at 20 to 24 months. By the time the child is 2 years old, all 20 primary teeth should be evident in the oral cavity (1,2,3).

Beneath the primary teeth, 20 permanent (succedaneous) teeth develop. As root development takes place in the permanent teeth underneath, this causes exfoliation of the primary teeth. Osteoclast formation is stimulated, which results in the resorption of the roots of the primary teeth and their subsequent loss. In addition, 12 permanent molars develop distally in sequential order: 3 upper and 3 lower on each side of the oral cavity (2).

With the exfoliation of primary teeth and replacement by permanent teeth, the child enters a mixed-dentition stage. Permanent teeth erupt in the following sequence: lower central incisor and first molars at about age 6 to 7, followed by the upper central incisor and lateral incisors, the canines and premolars, second molars, and finally third molars (wisdom teeth) during late teens up to the early twenties (1,2).

Disorders of tooth eruption and positioning are common pediatric dental problems that present clinically as malocclusion or abnormal alignment of the dentition. Delayed eruption of all teeth is indicative of developmental delay, hormonal abnormalities, and nutritional or systemic disturbances (e.g., hypothyroidism, trisomy 21, rickets, type I osteogenesis imperfecta, cleidocranial dysostosis, Albright osteodystrophy, progeria, or incontinentia pigmenti). Failure of eruption of single or small groups of teeth suggests local causes such as malpositioning of teeth, supernumerary (extra) teeth, retained primary teeth, or cysts (2,3). In contrast, premature eruption of all teeth is associated with precocious puberty or hyperthyroidism. Early emergence of single or small groups of teeth can arise from early loss of a primary tooth from trauma or extraction caused by caries and infection. An example of premature eruption is the presence of natal or neonatal teeth (at or within the first month of life) which are often rudimentary in form and appear as mere scales of enamel or shells of tooth crowns. They represent supernumerary teeth in approximately 15% of cases, and are frequently associated with other conditions (e.g., cleft palate, chondroectodermal dysplasia, pachyonychia congenita, Hallermann-Streiff syndrome) (2,3).

Other common pediatric dental issues related to developmental disorders of the dentition are abnormalities of tooth number, size, shape, structure, and color. Anomalies in tooth number are due to hereditary patterns producing extra or missing teeth, physical disruption of the dental lamina, and overactive dental lamina or failure of dental lamina induction, leading to an excess or failure of tooth initiation, respectively (3,4). For example, if the dental lamina produces an increased number of buds or if there are physical disruptions in the embryonic dental lamina, supernumerary teeth occur and the condition is termed hyperdontia. The extra teeth erupt most often in the maxillary midline between the central incisors. In contrast, when no tooth buds form (e.g., in congenital tooth absence) or when a normal site of initiation is disturbed (e.g., in cleft palate), the resultant reduction in number of teeth is termed hypodontia. The teeth that are most commonly absent are the third molars, the maxillary lateral incisors, and the mandibular second premolars (2,3,4).

Abnormalities in tooth size and shape occur as a result of disturbances during the morphodifferentiation stage of tooth development. Common examples are macrodontia, microdontia, and twinning. Macrodontia describes teeth that are larger than normal. Regional macrodontia is associated with hemifacial hyperplasia while diffuse macrodontia, a rarer condition, is associated with pituitary gigantism (2,5). Microdontia refers to a reduction in teeth size that is of hereditary genetic etiology. Localized microdontia is common, most frequently affecting the maxillary lateral incisors which may become slender and tapered (peg-shaped). Diffuse microdontia, which occurs

rarely, is associated with pituitary dwarfism (2,3,5). Twinning is the phenomenon in which two teeth are joined together, and may result from fusion (the union of two separate tooth buds due to pressure, trauma, or crowding, creating a tooth of increased size or a reduction in number), germination (the incomplete division of a single tooth bud resulting in malformed teeth), or concrescence (joining of the roots of adjacent malpositioned teeth) (2,3,4).

Abnormalities in tooth structure, namely defects in the enamel or dentin layers, result from disruption during the histodifferentiation, apposition, and mineralization stages of tooth development. Common pathologies that affect the teeth surfaces and alter their appearances clinically are amelogenesis imperfecta (AI) and dentinogenesis imperfecta (DI). AI is a hereditary enamel defect that manifests as hypoplasia or hypocalcification, in which either insufficient quantities of enamel are formed during the histodifferentiation state of tooth development or the calcification stage of enamel formation is defective (4). Because there is faulty production of organic matrix, the teeth are covered by only a thin surface of malformed enamel which is susceptible to fracture and abrasion. The clinical appearance could range from the teeth being small and discolored as the yellow underlying dentin layer is seen, to the surfaces being pitted, rough, and worn down by attrition (3,6). Some nutritional and systemic disorders that can adversely affect enamel formation are vitamin A, C, and D deficiencies, exanthematous diseases, congenital syphilis, birth injury, prematurity, Rh hemolytic disease, local infection or trauma, and ingestion of chemicals (e.g., fluoride and tetracycline) (2). The treatment of AI varies depending on the extent of enamel involvement. The main concern is the loss of tooth structure due to attrition, thus full prosthodontic coverage with crowns is usually recommended for the preservation of the teeth in function. For patients without sufficient tooth structure remaining, over-dentures are recommended to prevent further erosion of the teeth. A physician who recognizes AI in a patient should make the proper referral to a dentist.

DI is an analogous condition in which the hereditary defect is in the dentin layer and dentinal organic matrix. It may be seen alone or occur with osteogenesis imperfecta, an inherited defect in collagen formation resulting in osteopenic bones, bowing of the limbs, bitemporal bossing, and blue sclera (4,6). During the histodifferentiation stage of tooth development, odontoblasts fail to differentiate normally, leading to poorly calcified dentin. The defect in dentin structure alters the junction between enamel and dentin. The enamel layer tends to flake away easily from the underlying dentin, exposing it, leading to rapid attrition. The typical clinical finding of DI is a bluish, brown translucent discoloration. Unless the crowns of these teeth are covered early and completely, the abrasion of chewing often reduces them to the level and contour of the supporting alveolar bone (3,6). Additional causes of dentin abnormalities are systemic disorders that impair normal absorption and circulating levels of calcium and phosphorous, such as Vitamin D-resistant rickets and hypoparathyroidism. Regional vascular abnormalities may also arrest calcification of both dentin and enamel and hinder tooth development (4). Depending on the morphology of each tooth, the size and shape of the crowns and root canals, full coverage prosthesis or full dentures are recommended. In the long run, these patients may be candidates for dental implants as well (6).

Tooth color abnormality is another commonly encountered dental problem that can result from intrinsic or extrinsic staining. Intrinsic staining is due to the incorporation of foreign substances into the developing enamel, while extrinsic staining is superficial and due to adherence of plaque or other discoloring substances to the teeth. Causes of extrinsic stains include a variety of foods and beverages (e.g., coffee), chromogenic bacteria, and iron found in infant formulas and vitamin supplements. In contrast, intrinsic stains are caused by blood borne pigments (e.g, congenital porphyria, cholestatic disorders, anemias, hemolysis) which produces red-brown discoloration, neonatal hyperbilirubinemia which produces blue-black discoloration of primary teeth, drug administration during enamel formation (e.g. tetracyclines) which causes brown-yellow discoloration, and hypocalcified-hypoplastic disease states which manifest as opaque white patches on the tooth or pitted areas devoid of enamel (2,3,4). At concentrations higher than 2.0 parts per million (ppm), fluoride content in drinking water can also cause a variety of discoloration, ranging from small white patches to severe brownish mottled enamel when concentrations exceed 5.0 ppm (3,4). The discoloration of intrinsic stain requires bleaching to remove, whereas extrinsic stains, which are developmental in nature, can be removed with abrasive agents used in dental cleanings.

Dental emergencies are a common occurrence, with the majority of cases due to trauma or pain (e.g., from dental decay and infection). As many as 10% of children may suffer significant tooth trauma requiring emergency management. Dental trauma tends to occur in toddlers (ages 1-3) from falls or child abuse, in school-aged children (ages 7-10) from bicycle, scooter and playground accidents, and in adolescents (ages 16-18) from fights, athletic injuries, and vehicle accidents (3). Facial trauma may loosen, avulse, or fracture teeth. If the family has a regular dentist, this dentist can be called for advice and many will provide after hours emergency care in their office. Without a family dentist, the patient will probably seek care in an emergency room, most of which are not optimally equipped for dental care. A frequently encountered dental emergency is tooth avulsion. If it is a permanent tooth, it should be rinsed and immediately inserted back into the gum socket (unless the patient is too young to be cooperative); alternatively, it can also be stored in saliva, saline, or milk. The tooth should not be scrubbed. Immediate dental consultation should be obtained.

Dental decay (caries) is the most common chronic disease of childhood, particularly in children of low socioeconomic backgrounds, minority groups, and developing countries who have limited access to dental care. The prevalence of dental decay is 30% to 50% among poor and minority children, and as high as 70% in some Native American groups (3). Beginning at an early age, cavities affect nearly 20% of 2 to 4 year olds, more than 50% of 8 year olds, and greater than 75% of 17 year olds according to CDC surveys.

The decay process of dental caries is characterized by demineralization and breakdown of tooth organic matrix. The development of caries is a complex, multifactorial process dependent on the presence of dental plaque, specific acidogenic bacteria (primarily Streptococcus mutans), fermentable carbohydrates, and a susceptible host. Host factors that increase the risk of caries include decreased salivary flow rate and pH, as well as areas of defective tooth maturation (e.g., enamel developmental dysplasia) where incremental layers have been disturbed and become susceptible to decay (2,7).

Caries formation is precipitated by specific oral bacteria that utilize dietary carbohydrates, primarily sucrose, as a substrate for acid production via fermentation. The acidic metabolic products in turn demineralize the tooth by reducing the pH of the surrounding dental plaque. The acidogenic bacteria most commonly associated with dental caries is Streptococcus mutans. S. mutans is a gram-positive bacteria with the ability to adhere to dental enamel, survive at low pH, and produce abundant acid. Carious lesions first appear as opaque white to brown specks, but gradually progress to cavitations of the enamel surface, invasion by other acidogenic bacteria (e.g., Lactobacilli) that worsen the decay, and eventual loss of the tooth if the damaging course is not halted (2,3).

A key determinant of dental decay is the frequency of carbohydrate consumption, and not necessarily the quantity consumed. In other words, retaining sweets orally for prolonged periods or drinking sweetened beverages constantly is more cariogenic than consuming the same amount of sugar in a single meal (3). Hence, the terms baby bottle syndrome and nursing bottle caries have been used to describe the phenomenon of early childhood caries (ECC), which is rampant decay that arises from the poor habit of bed time bottle feeding in infants and toddlers (< age 3) combined with concurrent S. mutans infection. ECC usually damages the upper primary teeth, due to the

child's prolonged sucking on a bottle containing sweet juice or milk during sleep hours. The mandibular (lower) anterior dentition are usually spared because of their proximity to major salivary glands which help to neutralize the bacterial acid by-products (2,8).

Children with ECC are at increased risk for developing further caries with age. Furthermore, long standing untreated caries may lead to dental abscesses, resultant soft tissue swelling intraorally and/or facial swelling. Therefore, early diagnosis and prevention can help eliminate significant dental complications in toddlers and reduce the risk of decay in later childhood. Bottle feeding should be discontinued at 12 months. This may be unrealistic for some families, but it should certainly cease by 15 months of age. A physician who notices signs of baby bottle caries during a routine examination should refer the child to a dentist.

All parents should receive anticipatory guidance regarding dental development, oral hygiene, fluoride use, diet and feeding habits. Experienced primary care physicians can also perform a basic dental exam to screen for problems such as baby bottle caries, other caries, abnormal eruption sequence, and malocclusion. The American Academy of Pediatric Dentistry recommends an oral examination for all infants within 6 months of the eruption of the first tooth and no later than 12 months of age (9). Children at high risk for dental disease (e.g., low socioeconomic background, poor feeding habits) should receive checkups as often as every 3 months. While low risk children can be seen yearly, most children are recommended to receive periodic dental exams at 6 month intervals.

The use of fluoride represents the most promising approach to caries control. Fluoride plays a key role in altering the composition of the calcifying tooth structure, which changes the tooth's susceptibility to caries. The only mineral component in tooth is hydroxyapatite, a form of calcium phosphate easily substituted by other chemicals. When a high fluoride content is incorporated into the tooth structure, it becomes less soluble to the acid by-products of cariogenic bacteria. The American Dental Association recommends supplemental fluoride based on the concentration of fluoride ion (ppm) in drinking water (10). No supplemental fluoride is needed in newborns until age 6 months. For children between ages 6 months to 3 years, if the water fluoride concentration is less than 0.3 ppm, the supplement dose should be 0.25 mg/ day. No supplement is needed if the water fluoride concentration is greater than 0.3 ppm. In children between ages 3 to 6 years, if the water fluoride concentration is less than 0.3 ppm, the supplement dose should be 0.5 mg/day. If the water fluoride concentration is between 0.3 to 0.6 ppm, the supplement dose should be 0.25 mg/day. No supplement is needed if the fluoride concentration is greater than 0.6 ppm. In children between ages 6 to 16 years, if the water fluoride concentration is less than 0.3 ppm, the supplement dose should be 1.0 mg/ day. If the water fluoride concentration is between 0.3 to 0.6 ppm, the supplement dose should be 0.50 mg/ day. No supplement is needed if the fluoride concentration is greater than 0.6 ppm.

Community water fluoridation provides the most effective means for fluoride supplementation during the formative years of a child's growth. The water supplies for most communities in Hawaii are not fluoridated which is a major reason why children in Hawaii have one of the highest per capita rates of dental caries in the U.S. If community water fluoridation is not available, two other delivery systems of fluoride are available. Systemic fluoride can be prescribed for the child, usually in the form of sodium fluoride drops or tablets. Systemic fluoride incorporates itself into the developing teeth long before eruption. Topical fluorides are also available by prescription. Neutral sodium fluoride gel 1.1% or stannous fluoride 0.4% can be brushed on teeth or placed in a fluoride tray and applied to teeth for 3 to 5 minutes once a day. Excessive fluoride, however, can result in fluorosis which most commonly presents as dental discoloration (white and brown spots). Fluorosis may occur from excess fluoride intake due to swallowed fluoridated toothpaste or overaggressive fluoride administration.

Since good eating habits can be established in early childhood, parents should be educated and informed of the importance of limiting a child's consumption of foods with high sugar content, such as candies, honey, cookies, jam, chewing gum, jellies, sugary drinks and other adhesive carbohydrates. The child's frequency of eating is also an important contributing factor to the formation of carious lesions, especially the habit of eating in between meals and at bedtime. In addition to a sensible restriction of the child's sugar intake, the role of plaque in the caries process should also be discussed with the parents. Dental plaque is composed of densely packed microbial structures, insoluble salivary glycoproteins, microbial extracellular products, and epithelial and dietary debris which adhere firmly to teeth. It houses various bacterial populations. Dental plaque resists displacement by the forces of aqueous rinsing, but are readily removable by the mechanical actions of brushing, flossing and dental prophylaxis.

Brushing should begin as soon as teeth erupt, and reinforced by parents until children develop enough coordination required for adequate oral hygiene (usually until age 8). Unfortunately, it is common for parents to stop brushing their child's teeth when faced with a non-compliant youngster who throws a temper tantrum to avoid toothbrushing. Such parents must be taught that yielding is reinforcing the wrong behavior, as children soon realize that they can get away with brushing simply by crying. Instead, the opposite message should be conveyed. Children must understand that no matter how hard they resist, they will still need to get their teeth brushed. As long as parents are firm in enforcing toothbrushing routines, children will usually learn to accept it.

Prevention is optimized by regular dental examinations. Periodic dental visits familiarize the child with the dental office and offer the chance to develop a healthy rapport with the dentist, minimizing fear during future dental visits. More importantly, regular checkups enable early caries detection, application of topical fluorides, and reinforcement of home dental care instructions. Together, these preventive strategies help ensure the maintenance of good oral hygiene.

Questions

1. True/False: Normally, there are 20 deciduous teeth and 32 succedaneous teeth.
2. Name some developmental disorders of the dentition.
3. True/False: Amelogenesis imperfecta (AI) is a hereditary dental disease that can occur with osteogenesis imperfecta.
4. Which microorganism initiates the development of dental caries?
5. What are some preventive measures against dental caries?
6. At the 2 year old well child check, a child is noted to have severe decay of his anterior upper teeth. His mother claims that he stopped drinking from the bottle at age 12 months. His other teeth appear be normally formed. What is your comment to his mother?
7. A 10 year old boy falls off his bicycle and is struck in the mouth as he falls. His mother calls you for advice. He lost his front tooth and she has put it in a cup of milk. He did not loose consciousness. He is awake and alert and he does not appear to have other facial injuries. You advise her to call their family dentist to see if he can reimplant the tooth. In the meantime, what should his mother do with the avulsed tooth?

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9. http://www.cdc.gov/nohss/guideDV.htm

10. http://www.cdc.gov/OralHealth/factsheets/fl-supplements.htm

Answers to Questions

1. True

2. Disorders of tooth eruption and positioning (premature, delayed, or failure of eruption, malocclusion or abnormal alignment), abnormalities of tooth number (supernumerary tooth), size and shape (macrodontia, microdontia, or twinning), structure (AI or DI), and color (intrinsic or extrinsic staining).

3. False. Dentinogenesis imperfecta is the condition that may occur with osteogenesis imperfecta.

4. Streptococcus mutans

5. Fluoride supplementation, good oral hygiene that includes brushing and flossing, limiting the amount but more importantly the frequency of intake of sweets (especially the habit of bedtime bottle feeding, eating in between meals and at bedtime), regular dental visits.

6. It is very likely that this history is not correct. These appear to be baby bottle caries, which is the most likely cause. It may be that mother feels guilty that she is not following your advice so she is denying that the child continues to go to bed with a bottle. Another possibility is that she is giving the child juice in a bottle at night and does not consider this to be "bottle feeding". Grandparents living in the same household will often interfere with childhood rearing practices, since they may insist on letting the child have a bottle to prevent the child from crying.

7. The best thing to do with the tooth is to push it back into its original location after a gentle rinse, if the child is cooperative. Otherwise, the tooth can be placed in saline gauze or milk. The tooth should not be scrubbed.

Chapter II.1. Nutrition Overview
Caron M. Hong

This is a 4 month old boy who is not growing well. His birth weight was 3.5 kg and his current weight is 4.0 kg (less than the 5th percentile). Mother states that he drinks 6 ounces of infant formula every 4 hours (six feeding per day). She also feeds him a small amount of rice cereal, but he is having difficulty holding this in his mouth. There is no history of vomiting or diarrhea. He has about 6 wet diapers per day and stools once or twice daily. His review of systems is negative.

Exam: VS T 37.4 (rectal), P 110, R 30, BP 75/55, oxygen saturation 100% in room air. Weight 4.0 kg (less than the 5th percentile), height 57 cm (10th percentile), head circumference 41 cm (40th percentile). He is thin appearing, but not acutely ill. Head is normocephalic. Anterior fontanelle is flat and soft. HEENT is otherwise normal. Heart regular, without murmurs. His lungs are clear. His abdominal exam is normal. His genitalia are normal. His extremities are thin. His visible perfusion is good. Muscle tone and reflexes are normal.

Based on history, his fluid intake is calculated at 270 cc/kg and his caloric intake is calculated at 180 calories/kg, plus additional calories from rice cereal. His maintenance caloric intake should only be 100 cal/kg. Thus, it is estimated that his caloric intake is well in excess of maintenance nutritional requirements and he should be growing better than this. He is hospitalized for evaluation. Admission laboratories including a complete blood count and comprehensive chemistry panel are normal. He gains 100 grams daily for the first three days of hospitalization on formula alone, which is calculated at 280 cc/kg and 187 calories/kg. Since this is not much different from what he was getting at home (by history), the medical staff suspect that something in the history is not correct. Upon further questioning, mother was not feeding him 6 ounces of formula per feeding as she had initially stated. Instead, she was offering him some juice and she added extra water to the formula to make it go farther.

Nutritional requirements of infants and young children differ from that of adults in a number of aspects due to energy expenditure (i.e., basal metabolism, metabolic response to food, and physical activity), rate of growth, new growth, body composition, and physiological changes (e.g., puberty). Due to the high nutritional needs of infants and young children, there is an increased risk for nutritional disruptions (i.e., undernutrition and overnutrition). This risk may be compounded by lack of knowledge or awareness of signs and symptoms on the part of the caregiver. Regular well child care visits aid in the prevention and screening of such disruptions and can alleviate associated detrimental effects.

A good nutritional assessment includes a family history, developmental assessment, medical history (including growth history), and physical examination, especially growth parameters (Table 1). Anthropometrics is the measurement of the physical dimensions of the human body at different ages (1). Reference curves derived from the normal population are used to plot each child to monitor and follow development and growth. Anthropometric parameters include weight, length, head circumference and body mass index (BMI).

Table 1. Aspects of Nutritional Assessment
Dietary evaluation
Growth (weight, height, head circumference)
Upper arm and skinfold measurements (optional)
BMI (body mass index)
Additional corrections for:
- -gestational age (premature infants)
- -delayed/precocious growth (radiographic bone age)
- -sexual maturity (Tanner stage)

Clinical evaluation (medical history, physical examination and anthropometry)
Laboratory data (e.g., hemoglobin, iron, serum proteins) (optional)

The guidelines for nutritional requirements incorporate dietary reference intake values including recommended daily allowances (RDA) and adequate intake (AI) values. These values should be used as a guideline and should be modified as needed (e.g., rapid changes in requirements that occur during infancy). General nutritional requirements are based on age, body size, growth rate, physiological losses and caloric intake. Therefore, a child's rate and stage of growth usually parallels nutritional needs (including physical activity, body size, basal energy expenditure and state of illness). In infants, 9-15% of calories should be from protein, 45-55% from carbohydrate and 35-45% from fat. In older children, 10-15% of calories should be from protein, 55-60% from carbohydrate and 30% from fat. On average, carbohydrate and protein contains 4 calories per gram, while fat contains 10 calories per gram. Nutritional calories are actually chemistry kilocalories. Vitamin deficiency states are covered in a separate chapter.

Breastfeeding is recommended for newborns. Breast milk is the natural food for full-term and premature infants during the first months of life (1,2). There are nutritional, practical, psychological, immunological and physiological benefits to breastfeeding (refer to the chapter on breast feeding). Contraindications to breastfeeding include: mother receiving chemotherapy or radioactive compounds, maternal HIV/AIDS, active untreated maternal TB, maternal primary Herpes or Herpes in the breast region, certain medications (anti-thyroid drugs, chloramphenicol), use of alcohol and drug abuse.

It is strongly recommended by WHO (World Health Organization) that infants receive human milk exclusively through the first 6 months of life and that complementary foods are added thereafter through at least the 1st year of life (1). The alternative for human milk is infant formula based on cow's milk or soy protein (refer to the chapter on infant formulas). Human and cow's milk differ in composition with regard to protein, fat type and quantity of minerals and vitamins. Although technological advances have improved formula composition, formula still lacks the immunological advantages of breast milk.

Fluid maintenance can be calculated at 100 cc/kg/day for the first 10 kg, then 50 cc/kg/day for the next 10 kg, then 20 cc/kg/day thereafter. Maintenance caloric requirements can be estimated by the same numbers. Thus a 14 kg child has a maintenance fluid volume of 1200 cc/day and a maintenance caloric requirement of 1200 calories per day. The caloric density of infant formula is 20 calories per ounce (or 2/3 of a calorie per cc). Human breast milk has a variable caloric density, but it is usually less than 20 calories per ounce. Since the maintenance fluid and calorie calculations are the same, and formula is less than one calorie per cc, infants must take in more than maintenance volume in order to consume maintenance calories (i.e., for an infant to get 1200 calories per day, he/she would have to take in 1800 cc of formula). Growing and thriving infants must consume more than maintenance calories to cover maintenance needs plus the

requirements for growth. Thus, they will often consume 200 to 300 cc/kg/day of formula. The addition of solid foods after infancy which have a higher caloric density (calories per cc) permit them to consume more solids and less fluid in order to grow and thrive.

Maintenance caloric calculations are estimates. Clinical conditions associated with increased metabolic needs (e.g., congestive heart failure) or increased catabolism (e.g., burns), will have higher maintenance caloric needs. Conversely, clinical conditions which lower metabolism (e.g., paralysis), have lower caloric requirements.

By 6 months of age, babies' swallowing mechanisms have developed sufficiently enough for them to be started on solid foods. Toward the end of the 1st year (12 months), weaning from breast or bottle to cup use is advised. However, it is very common for children to continue to drink from bottles beyond this age. Children who continue to drink from bottles for prolonged periods (past 15 months of age) have a high incidence of dental caries and this practice possibly adds to the risk for otitis media. Dietary recommendations during growth and development are summarized below:

0-12 months: Vegetarian diet NOT recommended for the first 2 years of life. 2% or skim milk is NOT used since fat is needed for neural development (whole milk contains 4% fat, 2% milk contains 2% fat, skim milk contains no fat). Whole cow's milk is not recommended before 9 months of age (high renal solute load, poor protein ratio composition, poor Fe absorption and inappropriate energy distribution). Breast milk and/or formula can be used exclusively (no other foods are necessary) until 6 months of age. Some vitamin supplementation may be necessary (e.g., vitamin K given at birth, vitamin D to prevent rickets). Adequate iron intake must be assured (some formulas called "low iron", do not have enough iron). Daily fluoride supplements should be started at 6 months of age and continued until 12-16 years of age, to reduce the incidence of dental caries, in areas that lack fluoridation of the water supply (e.g., Hawaii).

6-9 months: This is the age at which solid foods are introduced. Iron enriched cereals (e.g., rice cereal) should be started first because they are less allergenic. New foods can be added gradually (only one to two new foods per week to determine hypersensitivity and/or food intolerance). Pureed yellow/orange vegetables (e.g., carrots, squash) should be added next. Pureed green vegetables should be introduced after yellow/orange vegetables because they have more bulk. Vegetables with high nitrite contents (e.g., beets, spinach, turnips) should be avoided. Vegetables are generally offered before fruits because the sweet taste of fruits may cause infants to reject other foods. Pureed fruits and juices, pureed meats, fish, poultry, and egg yolk can be introduced after the infant demonstrates tolerance to pureed vegetables. Avoid egg whites until 12 months because of the risk of allergy. Avoid desserts, since these have no significant nutritional value and their sweet taste may cause infants to reject other foods.

9-12 months: Finger foods, peeled fruits, cheese and soft cooked vegetables may be. Avoid peanuts and raw, hard vegetables until 3-4 years old, because of the risk of aspiration. Avoid added sugar, salt, fat or seasonings.

1-2 years: Eating habits formed from 1-2 years of life affect subsequent years. A vegetarian diet is not recommended for the first 2 years of life. Very soft table foods can be offered. High protein foods contribute to their growth potential. Carbohydrates and fats contribute to meeting their energy requirements.

2 years: Snacks may be included (e.g., juice and crackers), but this should be encouraged. This age (also known as the terrible two's) is typically associated with a decreased appetite (due to social interactions/refusal of food) and poor weight gain. Parents often unintentionally reward the wrong behavior. For example, if a child does not eat much at lunch or dinner, parents feel sorry for them and want them to grow, so the child is given a snack (e.g., cookies, chips, ice cream) between meals. Because these snacks are never as nutritious as what is served at dinner, and the snacks often taste better, the child learns that if he/she refuses lunch or dinner, they will get a better tasting snack later. Poor growth typically results. Parents unintentionally reward the child to eat poorly at mealtime (i.e., if you eat poorly at dinner time, I'll reward you by giving you ice cream and cookies later). Proper counseling advises parents to avoid all snacks. Even if the child refuses lunch or dinner, he/she must learn that there will be no food until the next meal. When this is practiced consistently and reinforced, they will eat well at meal time, which is when the most nutritious food is served.

2-5 years (toddler years): Restrict fat to less than 30% of calories (saturated fats <10%). This can be accomplished by switching to low-fat milk (2% or skim), low use of butter/margarine and removing visible fat from foods. Dietary choices expand to the adult range of foods (i.e., most table foods). Emphasize the importance of adequate protein in the diet. Vegetarians should be cautioned that the absence of all animal proteins may lead to a deficiency of vitamin B12. In addition, the quantity of protein in plant substances (e.g., soy) is small compared to that in meat, chicken, fish and eggs. Since the body is largely comprised of protein, strict vegetarians are less likely to gain height as fast as their non-vegetarian peers.

Childhood obesity is a growing and serious problem. The prevalence of type 2 diabetes among school aged children is increasing. There are no easy solutions, but dietary counseling to reduce fat and total calorie consumption at an early age when obesity is first detected is appropriate. Caloric consumption increases markedly in the pubertal period and adolescent years. Adolescent activity ranges from very active to very sedentary (TV, video games and computers have contributed to this). Sedentary individuals may actually consume more calories and are at high risk for obesity. In females, attention should be given to iron and calcium intake. Calcium intake during the time of accelerated growth and skeleton formation is an important factor in reducing the risk of osteoporosis decades later. During adolescence, it is important to recognize the potential for eating disorders such as anorexia and bulimia nervosa (see chapter on eating disorders). With the exception of eating disorders, adolescents are at higher risk of over eating rather than under eating. Dietary counseling during adolescence is likely to contribute to healthier eating habits as an adult.

Questions

1. True/False: Technological advances in formula have eliminated the immunological difference between human milk and commercial infant formula (cow's milk and soy protein).

2. True/False: Vegetarian diets are acceptable in a 1 year old child.

3. True/False: During the second year of life, there is a decrease in appetite and low weight gain as children follow normal growth curves.

4. Should fluoride be supplemented? If so, when and under what circumstances.

5. Which of the following is NOT true about breast feeding?
   a. Recommended food for infants both term and preterm
   b. 50% of energy from proteins
   c. Contains immunological benefits (i.e. IgA, active lymphocytes)
   d. Promotes growth of lactobacillus in GI
   e. Decreases incidence of allergic disorders

6. Is a 9 kg child who is consuming 8 ounces of formula 5 times a day, likely to grow? Calculate cc/kg/day, calories/kg/day. 1 ounce = 30cc. Formula contains 20 calories per ounce.

7. Calculate the total number of calories for a serving of chicken noodle soup: Serving size=4 ounces, total fat per serving=2 grams, total carbohydrate per serving 8 grams, total protein per serving 3 grams, total sodium per serving 890 mg. Calculate the total calories from carbohydrate, protein and fat separately.

8. A premature infant in the neonatal ICU weighing 850 grams is receiving total parenteral nutrition (TPN). He is getting intralipids 10% (10 grams per 100cc) at 1 cc/hr and a separate infusion at 5.5 cc/hr of crystalloid which contains D12.5% (12.5 grams of dextrose per 100cc) and 2 grams of amino acids per 100cc. How many calories from carbohydrate, protein and fat is the patient receiving per day? How many calories per kg is the patient getting per day? Is this enough to gain weight?

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Answers to questions

1. False. Formula still lacks the immunological advantages of breast milk.
2. False. Vegetarian diets are NOT recommended for the first two years of life.
3. True.
4. Yes, at 6 months in children in a community with a non-fluorinated water supply.
5. b. 50% of energy from FAT.
6. No, this child will lose weight (failure to thrive). This child is consuming 40 ounces per day which is only 800 calories per day. This child needs 900 calories (100 cal/kg/day) just for maintenance alone. Growth requires a caloric intake in excess of maintenance.
7. Roughly 64 calories. Protein=4 calories/gram, carbohydrate=4 calories/gram, fat=10 calories/gram. 12 calories from protein, 32 calories from carbohydrates, 20 calories from fat, no calories from sodium total calories=64 calories (roughly).
8. This child is receiving 10% (10 gram/100cc) intralipids at 1cc/hr, or 24 cc/day, which is 2.4 grams per day, which is 24 calories from fat per day. He is getting D12.5% (12.5 gm/100c) at 5.5cc/hr, or 132 cc/day, which is 16.5 grams of dextrose per day, which is 66 calories from carbohydrates per day. He is getting 2 grams of amino acids per 100cc, which means that he gets 2.64 grams of amino acids per day, which is 10.5 calories from protein per day. He is getting a total of 100.5 calories per day, which is 118 calories per kg/day. Since his maintenance caloric requirement is 100 calories/kg/day, he is getting more than maintenance which should give him the potential to grow.

Chapter II.2. Breastfeeding

Meta T. Lee, MD, MSEd

You are seeing a 7 day old infant for a routine post-nursery follow-up visit. The 18 year old first time mother is concerned that the baby is not eating enough. The infant is a normal full term male with no significant perinatal history. The baby drinks Enfamil 1-2 oz every 2-3 hours in addition to breastfeeding. She offers the baby the breast before each feed, but he either refuses to latch on or falls asleep after 5 minutes. When offered the bottle, he drinks about 1-2 ounces at a time. The mother complains that her breasts are full and tender, and that it hurts when the baby breastfeeds.

On review of systems, the baby is voiding 6-8 times a day, and stooling 4-6 times a day. There is no emesis, diarrhea, or excessive fussiness. FH is positive for allergies. The mother denies medical problems, denies prior surgeries, and is on no medications. SH is positive for a teen mother who lives with her parents. The father is not involved.

On exam, the infant is healthy appearing and has already surpassed his birth weight of 3700 grams. The exam is normal except for some mild jaundice to the face. The mother's breasts are hard, engorged, non-erythematous, and tender. Her nipples are cracked and bleeding.

You commend this mother on choosing breast milk as the preferred source of food for her infant. You reassure her that during the first six months of life, no additional liquids, foods, or vitamins are necessary for breastfed babies. You observe the baby and mother during a breastfeeding session in your office and explain that the pain experienced during breastfeeding is due to improper latch on. Improper latch on has also caused her nipples to crack and bleed, and resulted in inadequate excretion of milk. You explain to her that in order to maintain a good milk supply, milk needs to be removed from the breasts at least 8 to 12 times in every 24-hour period. You or your nurse teach her proper positioning and technique for proper latch on and refer her to the hospital lactation consultant for a next day appointment. You see her back in your office in 2-3 days and she reports that the baby is nursing much better and that her nipples and breasts are no longer painful.

Human milk is recommended as the optimal form of nutrition for infants (1). Breast milk contains the essential nutrition, immunomodulators, and anti-microbial agents for optimal growth and development. The AAP recommends exclusive breastfeeding to all infants in the first four to six months of life, and continued breastfeeding to at least the first year of life. However, national surveys report that 60% of women breastfeed postpartum, 30% exclusively breastfeed to six months of age, and an estimated 5% are still breastfeeding at 1 year of age (2). Although breastfeeding is the optimal nutritional source for growing infants, breastfeeding practices in this country are sub-optimal. Physicians can be influential in promoting and educating mothers about breastfeeding. This chapter presents a broad overview of basic concepts essential to understanding and promoting successful breastfeeding.

The breasts are paired mammary glands in which milk can be produced based on hormonal, psychological, and environmental influences. The smallest functioning unit of mature glandular tissue is the alveolus. Alveoli are composed of secretory acinar units, which are surrounded by myoepithelial cells. Myoepithelial cells form the contractile unit responsible for ejecting milk into ductal system. The ductal system is a branched pathway in which small ductules merge into larger ducts, which widen and drain into lactiferous sinuses. These collecting sinuses are located behind the nipple and the areola of the breast. Milk is transferred out of the lactiferous sinuses through multiple small openings on the nipple surface.

Lactogenesis begins during pregnancy. During pregnancy, breast size increases, as epithelial cells of the alveoli differentiate into secretory cells for milk production. Progesterone is responsible for the proliferation of glandular tissue and ductile development in breast tissue. Estrogen, placental lactogen, human chorionic gonadotropin, and human chorionic somatomammotropin also contribute to mammary gland growth during pregnancy. Prolactin is the primary hormone responsible for stimulating alveolar cells to produce milk. During pregnancy, high levels of progesterone inhibit prolactin from milk synthesis.

Hormonal changes occurring immediately after birth initiate the process of copious milk production. Following the delivery of the placenta, systemic levels of progesterone and estrogen drop steadily, while prolactin levels remain high. In addition, oxytocin, a hormone produced in the posterior pituitary, enables the milk-ejection or milk let-down reflex to occur. Tactile stimulus from the nursing infant releases oxytocin, which acts upon mammary myoepithelial cells to contract and force milk from the alveoli into the ducts toward the lactiferous sinuses where it becomes readily available for consumption.

The maintenance of milk production in lactation is dependent on systemic hormone regulation as well as autocrine regulation of the mammary gland. A peptide inhibitor in the mammary gland slows milk production unless it is removed by frequent nursing. Hence, lack of adequate milk removal results in stasis, and limited breast milk synthesis. Conversely, when frequent feeding occurs, the inhibitor is removed and milk production is increased. Hence, removal of milk from the breast facilitates continued milk production. This "supply-demand phenomenon" results in a feedback control mechanism that regulates the production of milk to match the intake of the infant. Human milk contains protein, non-protein nitrogen compounds, lipids, oligosaccharides, vitamins, minerals, hormones, enzymes, growth factors and other protective agents. The composition of human milk is considered the "gold standard" to which all formulas attempt to recreate.

The major carbohydrate constituent of human milk is lactose. Small quantities of oligosaccharides, galactose and fructose are also present. Lactose concentration in human milk is relatively constant at 7gm/dl. This value varies with maternal diet. Lactose enhances calcium absorption and metabolizes readily to galactose and glucose, which supply energy to rapidly growing organs such as the brain.

Casein and whey are the major protein constituents. Human milk is composed of approximately 30% casein protein and 70% whey protein. Whey protein consists of five major components: alpha-lactalbumin, serum albumin, lactoferrin, immunoglobulins, and lysozyme. The latter three elements contribute to immunological defense. Oligosaccharides, nucleotides, growth factors, and cellular components of human milk also enhance the infant's immune system. Immunoglobulin A is also excreted into breast milk, which provides specific passive immunity against foreign antigens to which the mother is exposed.

The fat content in human milk is variable, and fluctuates with gestational age, maternal diet, and lactation patterns. Fat accounts for about one-half of the caloric value of human milk. Triglycerides are the main fat constituent, and are broken down into free fatty acids and glycerol by the enzyme lipase. The lipid portion of human milk contains essential fatty acids, which are important for brain growth and development.

The vitamin and mineral contents in human milk vary with maternal diet and genetic influences. Fat soluble vitamins A, E, D and K are present in human milk. Human milk is a good source of Vitamin A, which is required for vision and the maintenance of epithelial structures. Colostrum is rich in Vitamin E, an antioxidant that protects cell membranes in the retina and lungs against oxidant-induced

injury. Vitamin D is present in low quantities in breast milk. Daily supplementation with Vitamin D is recommended to exclusively breastfed infants at risk for rickets. Infants at risk include children who are not adequately exposed to the sun and whose mothers who do not consume adequate nutrients. Vitamin K, required for the synthesis of blood clotting factors, is present in small amounts. Vitamin K supplementation in a single intramuscular injection at birth is recommended for all newborn infants even though it is normally produced in sufficient quantities by intestinal flora within a few days of birth.

Water soluble vitamins in human milk are very dependent upon maternal diet. Ascorbic acid, nicotinic acid, thiamine, B12, riboflavin, and pyridoxine (B6) levels increase with maternal ingestion of food containing these nutrients. Vitamin B12 is essential for early central nervous system development. Vitamin B12 supplementation should be considered for exclusive breastfed infants of strict vegetarian mothers.

The mineral content in breast milk is relatively constant. Sodium, iron, zinc, calcium, and other trace elements are present in human milk. Iron and calcium are present in small quantities in human milk, yet infants are able to absorb a greater proportion of these minerals than in cow's milk.

Advantages of breastfeeding

Human milk, through breastfeeding, provides nutritional, immunological, and developmental, benefits to infants. Studies have shown that human milk feeding decreases the incidence and severity of diarrhea, lower respiratory infections, otitis media, bacteremia, bacterial meningitis, botulism, urinary tract infections, and necrotizing enterocolitis (1). Limited studies also suggest a protective effect of human milk feeding against sudden infant death syndrome, insulin-dependent diabetes mellitus, Crohn's disease, ulcerative colitis, lymphoma, allergic diseases, and other chronic digestive diseases (1). There is also limited data that supports the potential for improved developmental outcome in certain breastfed infants at risk for developmental delay (3).

Mothers also benefit from breastfeeding. Increased levels of oxytocin result in more rapid uterine involution and less postpartum bleeding. Some recent studies also support that lactating women have an earlier return to pre-pregnancy weight, delayed resumption of ovulation with increased child spacing, improved bone remineralization postpartum, reduction of hip fractures in the postmenopausal period, reduced risk of ovarian cancer, and reduced risk of premenopausal breast cancer (1).

Breastfeeding also results in social, economical, and psychological benefits. Breast milk requires no preparation, hence increases time available to spend with the newborn. Lower incidences of infections in breastfed infants result in fewer days of work missed by parents. Families who breastfeed are relieved from a substantial financial burden incurred from the purchase of infant formulas throughout the first year of life. Last but not least, increased maternal-infant bonding is one of the major advantages of breastfeeding.

Clinical Approach

Preparation for breastfeeding should begin during pregnancy. An ideal time to discuss breastfeeding with the family is at the prenatal visit. A complete breastfeeding history includes a thorough discussion of the parents' intended method of feeding and the mother's previous breastfeeding history. A review of systems should include the incidence of previous postpartum hemorrhage and anomalies of the breast or nipple. Past medical history should include history of chronic medical illnesses, including seizure disorders, thyroid disorders, psychiatric disorders, or any other disorders requiring medications that may be contraindicated in breastfeeding. Past surgical history should include previous breast surgery, cardiac surgery, chest wall surgery, or breast trauma. A thorough medication history should be obtained. Family history should include incidence of breast cancer. Social history should include an assessment of the social support structure, as well as past or current history of illicit drug use and tobacco. Finally, questions the mother may have regarding breast changes during pregnancy or breastfeeding should be answered.

Breastfeeding is recommended as soon as possible after birth, preferably within the first hour of life. Immediate and sustained contact between mother and infant strongly correlates with longer durations of breastfeeding (4). During the first 48 hours of life, it is strongly recommended that a pediatrician, nurse, or lactation consultant observe and assist with at least one feeding in the hospital to document good breastfeeding technique prior to discharge. A follow-up visit is strongly recommended 48 to 72 hours after nursery discharge to ensure sustained adequate breastfeeding.

Anticipatory guidance should be directed at maintaining good breastfeeding technique, understanding signs of adequate intake, and forewarning new parents of the demanding and relentless feeding patterns of newborn infants.

Good breastfeeding technique requires proper positioning of the infant's body with proper "latch on", or attachment at the breast. An infant is in optimal positioning when the head and face are squarely in front of the breast, with the body in proper alignment with the head. Several positions of body alignment have been well described. In the "Madonna" position the infant lies across the mother's chest, with the infant's abdomen squarely facing the mother's chest. In the "football" position, the infant is "clutched" across the mother's side with the feet and body encompassing the side of the mother's body. In either position, the infant's head and body must be in proper alignment such that the infant is lying comfortably, with the mother's hand or arm firmly supporting the head.

An infant demonstrates good latch on when after properly positioned against the mother's body and triggered with an active rooting reflex, there is a wide opening of the jaw with relaxed lips that encompass contact beyond the nipple into the areolar space. Ensuring good latch on can prevent most common breastfeeding problems, such as sore nipples, engorgement, low milk supply, hyperbilirubinemia, and an unsatisfied baby.

Signs of good breastfeeding include the following: audible rhythmic swallowing during nursing, breasts feeling less full after each feeding session, at least 1-2 wet diapers per day for the first 2 days of life, 4-6 wet diapers every 24 hours after the 3rd day of life, and at least 3-4 bowel movements every 24 hours. Lack of persistent pain during breastfeeding sessions and absence of sore nipples are also signs of appropriate breastfeeding.

Anticipatory guidance on expected frequent feedings and nighttime awakenings can be helpful to new parents. Breastfed infants will often awake every few hours from hunger, and need to be fed at night to maintain growth. In addition, breastfeeding needs to occur at night in order to maintain adequate milk production. Hence, mothers should be prepared to expect to breastfeed newborns at least 8 to 12 times in a 24-hour period. Parents should also understand that newborns feed better when following their own sleep/wake cycles rather than when awakened around the clock. However, parents must understand that newborns in the first few weeks of life should be awakened if more than 4 hours pass between feedings.

Contraindications and Precautions

There are special conditions in which breastfeeding should not be recommended. Infants with galactosemia lack the essential enzymatic function to adequately digest the lactose component of human milk. Mothers with untreated active tuberculosis, human

immunodeficiency virus, human T-lymphocytic virus, or active herpes simplex virus on the breast can impose infectious health risks to breastfeeding infants. Breastfeeding should not be recommended in these instances.

Drugs given to mothers by various routes can also potentially affect a breastfed infant. The amount of drug that passes from the maternal bloodstream into human milk is variable and dependent on molecular size, pH of milk, pKa of the drug, fat solubility, and transport mechanisms. The amount of drug that reaches the infant's bloodstream is usually a very small percentage of the mother's dosage. Absolute drug related contraindications to breastfeeding include radioactive isotypes, antimetabolites, and cancer chemotherapy agents. There are a small number of other drugs, which have been shown to have potentially harmful effects on breastfeeding infants. All maternal drugs should be evaluated for breastfeeding safety through reference textbooks or local resources.

Previous breast or chest wall surgery is not a contraindication to breastfeeding (4). However, women who have had previous breast or chest wall surgery or trauma may have impaired lactation performance due to significant cutting of ducts or nerves important in the lactation process. Breastfeeding care should be individualized, and infants should be followed frequently for appropriate weight gain.

The American Academy of Pediatrics recommends that pediatricians promote and support breastfeeding enthusiastically. At the individual level, pediatricians are encouraged to take a strong position in favor of breastfeeding, as well as become knowledgeable and skilled in the physiology and clinical management of breastfeeding. At the local level, pediatricians are encouraged to work collaboratively with the obstetric and nursing community, promote hospital policies and procedures to facilitate breastfeeding, and become familiar with local breastfeeding resources. At the community and national level, pediatricians can also work to reform insurance coverage of necessary breastfeeding services and supplies, promote breastfeeding education as a routine component of medical school and residency education, and encourage the media to portray breastfeeding as positive and the norm.

Questions

1. What is the prevalence of breastfeeding in the United States?
2. What are the Healthy People 2010 goals for breastfeeding?
3. What is the American Academy of Pediatrics' position on breastfeeding?
4. What are the advantages and disadvantages of breastfeeding?
5. What anatomic and physiologic changes occur in the process of lactogenesis?
6. What is the difference between human milk and infant formula?
7. What are the barriers that prevent women from successfully breastfeeding?
8. What are some clinical indications that suggest inadequate or sub optimal breastfeeding?
9. What can health care providers do to improve breastfeeding practices for their patients?

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Answers to questions

1. Approximately 60% of women breastfeed immediately post-partum, 20% are still breastfeeding at 6 months, and less than 5% are still breastfeeding at 1 year.
2. The Healthy People initiative set a target to increase the proportion of mothers who exclusively breastfeed to 75% at post-partum, 50% at 6 months, and 25% at 1 year.
3. The AAP recommends exclusive breastfeeding for the first 4-6 months of life, with continued breastfeeding to at least 12 months of age, and thereafter for as long as mutually desired.
4. Advantages of breastfeeding include health, nutritional, immunologic, developmental, psychological, social, economic, and environmental benefits. The major disadvantages to breastfeeding include time and energy required of the mother, decreased paternal (father) participation, and lack of universal social acceptance of breastfeeding practices by the public.
5. Anatomic and physiologic changes that occur in the breast include: a) differentiation of epithelial alveolar cells into secretory cells for milk production. b) proliferation of glandular tissue and ductile development by progesterone. c) copious milk production following placental expulsion due to prolactin unopposed by progesterone. d) milk ejection or milk let-down reflex by oxytocin.
6. Carbohydrate, protein, and fat composition differ. Human milk contains lactose as the main carbohydrate source, high whey to casein protein ratio, and variable fat stores which are dependent on maternal diet. Formulas have variable carbohydrate source which include lactose, starch or other complex carbohydrates. Protein sources can also vary by formula type: casein, whey, soy or protein hydrolysate. Fat sources in infant formula can vary as well: triglycerides with long or medium chains, etc. Breastmilk has more absorbable iron, calcium and zinc than formula.
7. Barriers to successful breastfeeding include: physician misinformation and apathy, insufficient prenatal breastfeeding education, inappropriate interruption of breastfeeding, early hospital discharge, and late hospital follow-up care.
8. Indicators for inadequate breastfeeding include: less than 6 urinations per day and 3-4 stools per day by day 5-7 of life, decreased activity level, difficulty arousing, weight loss of greater than 15% of birth weight within the first week of life.
9. Provide good breastfeeding education at the prenatal visit, be well educated on anatomy and physiology of breastfeeding, advocate for breastfeeding policies.

Chapter II.3. Infant Formulas
Nadine Tenn Salle, MD

A 24 year old first time mother brings her two week old son to your office for a well child examination. She is a single mother with strong family support. She will be returning to work in one week and has elected not to breastfeed. Today she is seeking your advice concerning her infant's nutrition.

In a 1986 policy statement, the American Academy of Pediatrics (AAP) reaffirmed its position on four issues pertinent to infant nutrition (1):

1. The AAP will continue to promote breastfeeding as the first form of infant nutrition.
2. The AAP will continue to work to maintain and improve the high quality of infant formulas in the United States because in some cases, breastfeeding is not practical or desired.
3. The AAP will continue to recommend against direct to consumer advertising of infant formula.
4. The AAP will continue to encourage the special supplement nutrition program for women, infants and children (WIC) and hospital nurseries, and programs to make available a diversity of formulas.

The AAP adheres to the belief that pediatricians have a responsibility for infant nutrition, have an obligation to be knowledgeable about the nutritional needs of both healthy normally developing infants as well as infants with unique nutritional needs such as those with metabolic, gastrointestinal, infectious and oncologic disease conditions (1).

Breast milk is considered to be the optimal nutrient for the term or near term infant as an exclusive source of nutrition during the first six months of life. Breast milk combined with the introduction of solids is recommended for the second six months of an infant's life (2).

There are indications for the use of infant formula:

1. As a supplement or substitute for breast milk when a mother cannot or chooses not to breast-feed.
2. Infants whose mothers are infected with organisms known to be transmittable by human milk (e.g., HIV)
3. Infants whose mothers are undergoing chemotherapy.
4. Infants whose mothers are receiving medication or drugs that are excreted into human milk.
5. Infants who are unable to tolerate human milk because of metabolic disorders (e.g., galactosemia).

In the event breast feeding is neither practical nor desired, there are a number of commercially available infant formulas that have been formulated to simulate human breast milk and provide an infant's nutritional requirements. On average, a neonate will drink about 165 cc of formula/kg/day (2.5 ounces/pound/day) and about 30-90 cc (1-3 ounces) per feeding. The caloric content of most infant formulas closely approximates that of human milk at 2/3 kcal/cc (20 kcal/oz). Infants are often their own best regulators, thus variation with each feeding should be expected. During the first 6 months of life, infants require 95-115 kcal/kg/day; 8-12% of these calories should be derived from protein, 30-50% from fat and 40-60% from carbohydrates. If these nutritional requirements are met, an infant will typically gain 25-40 grams per day (30 grams = 1 ounce) in the first 3 months and 15-20 grams in the second 3 months. Infant formulas are designed to mimic the nutritional composition of human milk, but in reality they contain a number of differences in the protein, fat and carbohydrate content.

Human milk contains approximately 1.1 g/dL of protein as compared to 1.5g/dL in most standard formulas. This represents 6-8% of an infant's total caloric intake. Milk protein can be divided into two classes based on relative solubility in acid: whey (acid soluble) and casein (acid insoluble). The whey:casein ratio of human milk is 70:30 as compared to a ratio of 18:82 for cow milk. The clinical significance of the difference in whey:casein ratio between human and bovine milk is illustrated when unmodified casein-predominant cow milk enters the acidic environment of the human stomach and forms a relatively hard curd of casein and minerals. This curd can be difficult for an infant to digest. Thus, the AAP recommends that cow's milk not be used until after the first birthday. Special toddler's milk is now being marketed as a transitional formula to whole cow's milk; however there are no proven special benefits compared to a toddler eating a balanced diet that includes milk and juice.

Lipid constitutes approximately 50% of the calories in human milk (5.7g/100 kcal) and standard infant formula (4.4-6.0g/100 kcal). The predominant portion of lipid in human and cow milk is triacyl glycerol. Triacyl glycerol is composed of a glycerol backbone with 3-hydroxyl group esterified to fatty acids.

Essential fatty acids lineoleic and alpha lineolinic acid play a crucial role in neurodevelopment. Approximately 5-7% of total calories in human milk and 1% of total calories in cow milk is lineoleic acid. The amount of lineoleic acid considered adequate is controversial but it in generally agreed it should not be more than 20%. For this reason all cow milk based formulas add vegetables oil (containing relatively large amounts of lineoleic and lineolinic) to their preparations. Most commercial infant formulas contain at least 10% of total fatty acids as lineoleic acid.

The primary carbohydrate source found in both human milk and formulas is lactose (except in lactose free formula). Lactose is a disaccharide that is converted to simple sugars, galactose and glucose by a lactase enzyme. Disaccharides require conversion to simple sugars to enable absorption through the gut via a monosaccharide transport system. The carbohydrate source in soy based formula is glucose polymers (also referred to as corn syrup solids) and/or sucrose. Sucrose is converted to simple sugars, fructose and galactose for absorption (3).

The iron content of human milk is much less than that of iron fortified cow milk based formula, but the bioavailability of human milk iron is much higher. Guidelines from the committee on nutrition of the AAP recommends 2-3 mg/kg/day of elemental iron. In a term infant, iron deficiency is uncommon before 4-6 months of age because of the abundance of iron stores at birth. Iron deficiency is most common among children 6 months to 3 years of age. To compensate for the depletion of iron stores by growth, dietary iron must be provided. Exclusively breastfed infants may require diet supplementation with iron (1 mg/kg/day) and vitamin D (400 IU/day) at 4-6 months of age. Standard formulas (about 32 ounces per day) will meet 100% of RDA for vitamins and minerals for term infants. Low iron formulas defined by the FDA as containing less than 6.7 mg/L of iron, once contained less than 1.5mg/L of iron, resulting in an unacceptably high rate of iron deficiency and anemia. Over the past five years, formula manufacturers have increased the amount of iron in low iron formulas to 4-5mg/L. A public perception that iron causes constipation and other feeding problems has allowed for the

continued market of low iron containing formulas. There is no data to support this belief and the AAP recommends iron-fortified formulas.

Symptoms of cow milk protein allergy typically begin between week 4 to 6, but the sensitivity may occur as early as 48 hours or may present in adulthood. The presence of gastrointestinal symptoms such as bloody stools, diarrhea and vomiting can indicate pathophysiological intolerance related to a specific component of cow milk formula. Symptoms such as flatus, fussiness and colic are less likely and difficult to directly relate to components of cow milk. True cow milk protein allergenicity as documented by a double-blinded study is present in less than 6% of the population (5,6). Some surveys show as high 30% of formula fed infants are switched to hypoallergenic formulas because of a perceived or suspected protein allergy (7). Hypoallergenic formulas are created by extensively hydrolyzing the cow milk protein (usually casein), thereby reducing its molecular weight to less than 1250 kDa. Proteins less than 1250 kDa are far less likely to produce a IgE-mediated allergic response (6). Hypoallergenic hydrolyzed casein formulas are effective in preventing protein allergy. It is however prudent to truly diagnose cow milk allergic infant before starting these formulas whose most significant disadvantage is a greater cost when compared to regular formula. Breastfeeding is even more strongly advocated in infants with milk hypersensitivity.

Primary lactose intolerance such as lactase deficiency and galactosemia, occurs approximately in 1:1000 infants. Secondary lactose intolerance by contrast is far more common and often presents with protracted diarrhea. The lactase enzyme is located at the villous tip of the intestine and appears to be more vulnerable than sucrase that is found deeper in the crypt. An infectious diarrhea may cause denuding and the lactase enzyme may take up to a week to fully recover. A low lactose or lactose free formula may reduce carbohydrate malabsorption (and subsequent exacerbation of diarrhea by an osmotic mechanism) during the illness. The lactose free cow-milk based formulas are designed to treat primarily secondary lactase deficiency. The contrast to lactose containing formulas is the substitution of its carbohydrate source. Instead of lactose, a corn syrup solid and/or sucrose is used.

Soy formulas support the growth of normal term infants through the first year of life. Soy formulas may be used in lieu of cow milk formula and in formula fed infants whose parents want their children to adhere to a vegetarian diet. Phytate in soy formula in addition to the absence of lactose diminish the absorption of divalent cations such as iron, calcium and zinc in the intestinal lumen. Supplementation of soy formula with iron, calcium and zinc has largely overcome these issues (8,9). Phytogens in soy formulas have the potential for hormonal action at critical points in development. The AAP has noted that limited human data does not support these concerns (10).

Summary of formulas:

Cow's milk based formulas:

Indications: Term or near term infant.
Protein: whey-predominant; carnitine and taurine usually added.
Carbohydrate: lactose.
Fat: vegetable oils.
Brands: Enfamil with iron, Similac with iron, Good Start (100% whey protein, thus may be used for constipation), Lacto-free (uses corn syrup and/or sucrose), Similac PM 60/40 (60:40 ratio of whey to casein, less Ca, P, K for cardiac and renal patients).

Soymilk based formulas:

Indications: Lactose deficiency or galactosemia, strict vegetarians, IgE mediated reaction to cow milk protein.
Protein: 2.2g/dl of protein from a plant source, cysteine and taurine as well as an additional methionine added.
Carbohydrate: corn syrup (glucose polymer), sucrose.
Fat: vegetable oils.
Brands: Isomil, ProSobee.

Casein Hydrosylate formulas:

Indications: Milk or soy protein intolerance, colic.
Protein: casein hydrolysate (hypoallergenic).
Carbohydrate: glucose oligosaccharides modified cornstarch.
Fat: MCT, corn oil.
Brands: Pregestimil, Nutramigen, Alimentum (increased MCT fat concentration; for cystic fibrosis patients).

Questions

1. The American Academy of Pediatrics recommends what form of nutrition for infants?
2. What is an appropriate quantity of formula for an infant?
3. When is iron supplementation required for an infant?
4. When comparing breast milk vs. cow's milk based formulas, which has a higher: a) kcal/cc? b) Concentration of casein protein? c) Carbohydrate content? d) Fat content?
5. What is the clinical significance of the whey:casein ratio in cow milk?
6. What is the main form of carbohydrate in breast milk? Cow's milk based formula? Soy based formula?

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Answers to questions

1. Breastfeeding is regarded first and foremost except when it is not practical, desired or medically contraindicated.

2. From a practical standpoint, whether it is breast milk or infant formula, a healthy term infant is the best regulator of the frequency and quantity of their nutritional intake. However, since we are scientists at heart; during the first 6 months of life approximately 95-115 kcal/kg/day is recommended.

3. In a term infant, iron deficiency is uncommon before 4-6 months of age because of the abundance of iron stores at birth. To compensate for the depletion of iron stores by growth, dietary iron must be provided to exclusively breastfed infants. Iron fortified formulas can prevent iron deficiency in formula fed infants. Guidelines from the Committee on Nutrition of the AAP recommend 2-3 mg/kg/day of elemental iron.

4a. They are about the same. Human milk contains approximately 2/3 kcal/cc (20 kcal/oz). The standard infant formula usually remains close to this range.

4b. Whey:Casein of human milk is 70:30 as compared to a ratio of 18: 82 for cow milk. Please refer to the text to review the clinical significance of this profile difference.

4c. The carbohydrate content is about the same.

4d. Lipids constitute approximately 50% of the calories in human milk (5.7 g/100kcal) and standard infant formula (4.4-6.0 g/100kcal).

5. The clinical significance of the difference in whey:casein ratio between human and bovine milk is illustrated when unmodified casein-predominant cow milk enters the acidic environment of the human stomach and forms a relatively hard curd of casein and minerals. This curd can be difficult for an infant to digest. Thus, the AAP recommends that cow's milk not be used until after the first birthday.

6. Lactose is the main carbohydrate in mammalian milk. The lactose concentration of human milk is 7g/dL, cow milk contains 5 g/dL. Lactose is added to most standard infant formula to achieve the concentration of human milk. Soy formulas do not contain lactose; they contain sucrose, glucose polymers, or a mixture of the two.

Chapter II.4. Fluids and Electrolytes
Loren G. Yamamoto, MD, MPH, MBA

Case 1: A 4 year old male presents to the emergency department with a history of vomiting and diarrhea. He has had 10 episodes of vomiting (clear then yellow tinged) and 8 episodes of diarrhea with some mucusy material in the first few episodes. The diarrhea is now watery and the last few episodes have been red in color. The diarrhea odor is very foul. He has had a fever with a maximum temperature measured at 101 degrees at home. His parents gave him a sports drink (red color), and then they tried clear Pedialyte. Despite this, he continues to have vomiting and diarrhea. He feels weak and tired and he looks slightly pale at times. He has only urinated twice in the last 15 hours.

Exam: VS T 38.2 degrees (oral), P 110, R45, BP 90/65, oxygen saturation 100% in room air. Weight 18 kg. He is alert and cooperative, but not very active. He is not toxic or irritable. His eyes are not sunken. TMs are normal. His oral mucosa is moist but he just vomited. His neck is supple. Hear and lung exams are normal except for tachycardia. His abdomen is soft and non-tender. Bowel sounds are normoactive. He has no inguinal hernias and his testes are normal. His overall color is slightly pale, his capillary refill time is 2 seconds over his chest, and his skin turgor feels somewhat diminished.

He is clinically assessed to be 5% dehydrated by clinical criteria. Oral versus IV rehydration is discussed with his parents who indicate that they have tried oral hydration and are not happy with the results. They now have emesis on their furniture and carpet and he has splattered some diarrhea over the bathroom floor, so they would like the IV for him. An IV is started and a chemistry panel is drawn at the same time. A rectal swab for culture is also obtained. Normal saline is infused at 360 cc/hour for two hours (total of 720 cc). The resident on the case questions the high IV rate. It is pointed out that 360 cc is only 20 cc/kg which replaces only 2% of the body's weight (i.e., it corrects 2% dehydration), it doesn't include maintenance fluids, and 360 cc is the same volume as a soft drink can. He is also given ondansetron (Zofran) for nausea relief. His chemistry panel shows Na 135, K3.4, Cl 99, bicarb 15. During the first hour of the IV fluid infusion, he says that he feels much better. He more awake and his color improves. During the second hour of IV fluid infusion, he falls asleep. At the end of the two hours, he is awakened and since he feels better, he is discharged from the ER with instructions to rest and continue oral hydration efforts.

Three days later, his rectal swab is growing Salmonella. His parents are called. They indicate that he still has some diarrhea, but only about two episodes per day and his vomiting has stopped. He is on a regular diet and continues to improve. Because he has improved, no antibiotic treatment is started. However, vigorous hand washing and hygiene regarding dishes/utensils for all family members is recommended.

Case 2: An 18 month old female is directly admitted to the hospital from her primary care physician's office. She has had 15 episodes of diarrhea and 5 episodes of vomiting. She has a fever with a maximum temperature of 102.4 degree measured on a tympanic thermometer. She is weak, pale and her eyes are sunken. Her weight in the office is 11.0 kg which is decreased from her weight in the office of 11.6 kg just three days ago during a well child check. Urine output is difficult to assess because of the diarrhea.

Exam: VS T 37.8, P 110, RR 40, BP 100/60, oxygen saturation 100% in room air. Weight 11.0 kg. She is alert, but subdued and quite. She is not toxic and not irritable. Her eyes might be slightly sunken. Her oral mucosa is sticky (tacky). Her neck is supple. Heart regular, no murmurs. Lungs are clear. Abdomen is scaphoid, soft and non-tender with hyperactive bowel sounds. No inguinal hernias are present. Her skin turgor is diminished, but no tenting is present. Capillary refill time is 3 seconds over her thighs. Her extremities are cool in her feet, but warm elsewhere.

An IV is started and a chemistry panel is drawn. A stool rotavirus rapid assay is done which is positive. She is given 220 cc of normal saline IV over one hour and she feels much better. The appearance of her eyes have normalized and she is more active. Her chemistry panel shows Na 134, K 3.4, Cl 97, bicarb 12. The resident then writes the following IV orders: IV D5-1/3NS+20 mEq KCl per liter run at 88 cc/hour for 8 hours, then 66 cc/hour for 16 hours. She is also permitted to eat and drink small amounts, so a low fat diet without fruit juice is ordered for her. The medical student following the case asks how these IV orders are determined.

Since children are small, critical attention must be paid to fluid and electrolyte balance. An fluid administration could result in clinically significant overhydration, underhydration, or electrolyte imbalance. Normal humans will consume fluids and nutrients in response to their body's needs and regulation occurs automatically without any thought to this process. However, in pathologic conditions such as gastroenteritis, burns, neurologic dysfunction, etc., fluid losses may be excessive and the body's ability to respond to these deficits may not be intact. The purpose of this chapter is to familiarize the reader with normal fluid and electrolyte requirements. Much of this chapter consists of numbers, some of which should be memorized for personnel who provide medical care to children frequently. These will be called everyday basic numbers and are summarized in a table at the end of this chapter. Other numbers can be looked up in references when the need arises.

Body composition is 60% to 75% water. The 60% applies to adults and the 75% applies to newborns. Younger children have more water than adults. These numbers are estimates because body fat variations will modify these percentages as well (obese individuals have lower body water percentages). Out of this, about 60% is intracellular and 40% is extracellular. Of the extracellular fluid, 3/4 is interstitial and 1/4 is circulating as plasma (1). There is also a small percentage known as transcellular water (about 2%) which consists of synovial fluid, pericardial fluid, pleural fluid, bowel secretions, cerebral spinal fluid, etc. (1). This can be summarized below as:

Total body water: 60%-75% of body weight
- Intracellular: 30%-40% of body weight
- Extracellular: 20%-25% of body weight
  - Interstitial: 15% of body weight
  - Plasma: 5% of body weight

However, total blood volume is actually 8% to 9% of body weight for children and 7% of body weight for adults (2). This is because the red blood cell elements of blood are not considered to be "body water". Thus, if plasma consists of 5% of the body weight, a few more percentage points would account for the circulating blood volume (which is larger than the circulating plasma volume).

Fluid losses occur routinely through urine, stools, respiratory vapor and insensible skin losses. Perspiration can exaggerate skin losses. Illness and exercise can exaggerate respiratory fluid loss through vapor. Other conditions such as burns, vomiting, diarrhea, hemorrhage, diuretics, etc., can also exaggerate fluid losses.

Maintenance fluid volume for 24 hours can be calculated as follows: 100 cc/kg for the first 10 kg of body weight, 50 cc/kg for the next 10 kg of body, then 20 cc/kg thereafter. Thus, the maintenance fluid volume 40 kg patient would be calculated as: 10kg X 100 cc/kg + 10kg X 50 cc/kg + 20kg X 20 cc/kg = 1000cc + 500cc + 400cc = 1900cc per day. A shortcut for patients over 20 kg is to take 1500 cc and then add 20 cc/kg for additional weight above 20 kg. Maintenance electrolytes are calculated using maintenance fluid volumes as 3 mEq Na (sodium) and 2 mEq K (potassium) per 100cc of maintenance fluid. Thus, the 40 kg patient above would require 57 mEq Na (3 X 19) and 38 mEq K (2 X 19) per day.

This is translated into an IV rate in cc/hour by dividing the total volume of fluids by 24 hours. To deliver 1900 cc of fluid over 24 hours, the IV rate would have to be 80 cc/hr (roughly 1900 divided by 24).

The type of IV fluid is dependent on the electrolyte requirements. IV fluid basically comes as percentage of normal saline. Normal saline contains 0.9 grams of NaCl per 100 cc of fluid (0.9%). This is roughly 150 mEq of Na per liter. I remember this because I know that the body's normal osmolarity is 290 (or about 300). If "normal" saline has a "normal" osmolarity, then it's osmolarity must be about 290 mosm/liter. Therefore, half of its osmolar particles must be Na (sodium) and the other half must be Cl (chloride) to give a total osmolarity of about 300. Therefore, the concentration of Na (sodium) in normal saline (NS) is about 150 mEq/liter and the concentration of chloride in NS is about 15 mEq/liter. Half normal saline contains 75 mEq/liter. 1/3NS contains 50 mEq/liter and 1/4NS contains about 38 mEq/liter. It turns out that this is not exact. I could provide you with a table with the exact numbers, but no one can remember these. Fortunately, when selecting IV fluids, we just need to know approximate numbers. Therefore, following the rule of using "normal saline" permits one to know the approximate sodium concentrations of all IV fluids. Lactated Ringer's solution (LR) is similar to NS, but it also contains some potassium, lactate and calcium. Since LR also has a "normal" osmolarity, it will have less Na than NS in order to maintain its normal osmolarity. LR resembles the blood more physiologically. LR's electrolyte concentrations are Na 130 mEq/liter, K 4 mEq/liter, Cl 110 mEq/liter, lactate (similar to bicarbonate) 28 mEq/liter.

Since maintenance electrolytes are based 3 mEq Na and 2 mEq K per 100 cc of maintenance IV fluid, this will require a solution with 30 mEq Na per liter. The closest to this is 1/4 NS with about 38 mEq/liter. Potassium is always added as a separate electrolyte to the bag (with the exception of LR which already contains small amounts of potassium). The IV order that would be written for maintenance fluids on a 40 kg patient would be: IV D5-1/4NS + 20 mEq KCl per liter run at 80 cc/hr.

What exactly does maintenance mean? If the IV order above was accidentally written for 40cc/hr, would the patient become dehydrated? Alternatively, if the IV order was accidentally written for 200 cc/hr, would the patient develop pulmonary edema? If the IV order was instead written for D5NS (instead of D5-1/4NS), would the patient become hypernatremic? The answer to all of these questions is no (most of the time). By calculating the maintenance fluid volume for a 75 kg average adult, the maintenance volume would be 1500 cc + 55 kg X 20 cc/kg = 3000 cc. 30 cc is roughly one ounce. That's roughly 100 ounces, i.e., about 3 quarts or 8 soft drink cans per day. As an average busy adult, I normally do not drink this much, yet I do not become dehydrated. Also on some days, I consume a lot of salt (potato chips, etc.) and on some days I don't consume much salt. Yet my serum Na level stays in the normal range. If I drink an excess of fluid, my kidneys urinate more free water and if I don't drink much, my kidneys retain water and I don't put out much urine. Normal kidneys are able to compensate for wide ranges of fluid and electrolyte intake. Excess fluid and electrolyte intake is urinated out as excess, while inadequate intake results in renal retention of fluid and/or electrolytes to maintain normal fluid volumes and electrolyte balance. The

kidney has to do some work to remove excess substances or to retain substances which are in short supply. Renal consumption of ATP can be used as a marker of the amount of work performed by the kidney. Renal ATP consumption is high when excess fluid is consumed because it must work to excrete free water. Renal ATP consumption is high when insufficient fluid is consumed because it must work to retain water. In contrast, renal ATP consumption is low between these extremes because the kidneys do not have to work as hard. ATP consumption is lowest when the maintenance volume is consumed. Thus, maintenance volumes and electrolytes are beneficial because this results in minimizing the stress and workload on the kidneys. This is not very important in healthy individuals going about their everyday lives, but it becomes more important in very ill patients whose bodily functions are under great stress. Maintenance calculations using the formula provided are only valid under the assumption of the "average hospital patient". Some well people (e.g., while playing in a soccer game) will require more fluids than the maintenance calculation to minimize renal ATP consumption, while some well people (e.g., while reading a book) will require less fluids than the maintenance calculation to minimize renal ATP consumption. Special patients (e.g., severe burns) will require larger volumes of fluids to maintain fluid balance. Thus, the "maintenance" calculations provide a basic guide to determine the fluid and electrolyte intake that minimizes work stress on the kidneys of average hospital patients.

Although oral electrolyte solutions are commonly utilized for rehydration, they are actually maintenance electrolyte solutions. The most commonly recommended oral electrolyte solution known as Pedialyte contains 45 mEq Na per liter and 20 mEq K per liter. Sports drinks such as Gatorade have less sodium than this.

When a fluid deficit state is encountered, assessment of the severity is usually categorized as percent dehydration, which is really the volume of fluid loss as a percentage of body weight. Mild dehydration is 5% or less, moderate is about 10%, and severe dehydration is about 15% or greater. This classification is relative and not well standardized. Ideally, one could use their baseline body weight to determine the percentage of fluid loss, but this is almost never useful because growing children almost never have a known baseline body weight just prior to becoming ill. Additionally, factors such as anorexia and the duration of illness may lead to loss of lean body mass as well which adversely affects the weight calculation. Clinical and laboratory criteria have been developed to estimate dehydration percentage categories, but these are similarly flawed. Unfortunately, there is no certain way to accurately determine the degree of dehydration, therefore all clinical information (including weight loss if known) should be used to ESTIMATE the dehydration severity.

Criteria for 5% dehydration include: no tears when crying, oliguria, sticky (tacky) oral mucosa, less active than usual. Criteria for 10% dehydration include: sunken eyes, diminished skin turgor. Criteria for 15% dehydration include obvious shock (tachycardia, hypotension, cool extremities) and skin tenting. It should be noted that early signs of shock may appear as early as the 5% dehydration level. All of these clinical criteria have some flaws and they are not universally agreed upon. It is often not possible to estimate the urine output because of frequent diarrhea. The oral mucosa may appear to be moist if the patient has just vomited. Sunken eyes may be hard to determine if you don't know what the patient normally looks like. This is best assessed by asking the parent if the eyes look different. Parents will often use the word "hollow" to describe sunken eyes. A ketotic odor to the breath may signify ketosis due to poor oral intake which somewhat correlates with dehydration.

The serum bicarbonate is a measure of metabolic acidosis, but this can be misleading as well since sodium bicarbonate can be lost directly from diarrhea. However, an increased anion gap (calculated as Na minus Cl minus bicarb, which should be less than 12) is almost always present in clinically significant dehydration since lactic acid is produced in a dehydrated state (due to cellular hypoperfusion and a relative increase in anaerobic metabolism). This requires some thinking. For example, in vomiting patients, their bicarbonate initially increases (because of gastric acid loss resulting in a metabolic alkalosis); however, as fluid loss continues, they become dehydrated and a metabolic acidosis would indicate the presence of dehydration. In a patient with diarrhea, the bicarbonate value may be low from diarrheal losses of bicarbonate. So if the serum bicarbonate is relatively low and an increased anion gap is not present, this may not signify dehydration. However, the presence of an increased anion gap would indicate the presence of lactic acid production and dehydration. Similarly in diabetic ketoacidosis, the production of ketoacids and lactic acid results in an increased anion gap. Other clinical situations could affect the bicarbonate value and the anion gap in unusual ways, but this discussion is beyond the scope of this chapter. The above examples pertain to gastroenteritis only.

Replacing the fluid deficit (i.e., rehydration) can be done via oral rehydration or IV rehydration. Rehydration via a nasogastric tube is theoretically possible, but this option is not very popular since it possesses some of the negative characteristics of both oral and IV options. Oral hydration is generally preferable since this can be done at home, it is less invasive and it requires less costly resources. The AAP has published a practice guidelines on the management of acute gastroenteritis (3). Oral rehydration has been demonstrated to be successful in most (or perhaps nearly all) cases of gastroenteritis. The oral rehydration solution (ORS) developed by the World Health Organization takes advantage of the principle that glucose and sodium are co-transported in equimolar quantities across the GI mucosa. ORS contains this balance to optimize fluid absorption during gastroenteritis. Glucose in excess of sodium may remain in the bowel lumen as an unabsorbed osmotic particle which retains fluid in the bowel and inhibits fluid absorption.

ORS has been demonstrated to be efficacious even in children who are vomiting. The standard strategy is to give a small amount of fluid at a time. Giving 5 cc every 1 to 2 minutes reduces the volume remaining in the stomach at any given time. Since the stomach is similar to a bag, it is difficult for the stomach to vomit if only a small fluid volume is present. Giving 5 cc every minute results in a maximum fluid administration rate of 300 cc per hour, but this is very labor intensive for parents who must do this continuously for it to work. More commonly, 30 cc (1 ounce) is given every 15 minutes which results in a maximum fluid administration rate of only 120 cc per hour. This is more within the realm of what most parents are willing to do at home. If the child is not vomiting, then ORS can be given ad lib. It should be noted that a major difference between the clinical utilization of oral rehydration in the U.S. and other countries, is that American parents are very different from parents in much poorer countries. While parents in other countries may be willing to administer 5 cc every 1 to minutes, while the child continues to have a few emesis episodes, American parents are not likely to be this persistent. Often, if their child is not tolerating 30 cc every 15 minutes, American parents will frequently utilize the option of going to an emergency department for IV rehydration. Children in poorer countries do not have this option and despite sustaining greater degrees of dehydration, they are satisfactorily rehydrated via the oral route. It can be said that oral rehydration usually works for parents who are willing to persevere. In poor countries where an IV is rare, rehydration with ORS is life-saving to a very large number of children. In the U.S. severe dehydration is less common (better hygiene and nutrition), yet IV rehydration is used frequently for mild dehydration.

ORS is somewhat distasteful because it is rather salty and not very sweet. Even Pedialyte with much less sodium than ORS, is not very good tasting despite flavoring it. Significantly dehydrated children will usually drink ORS. Children who are not very dehydrated are not thirsty enough to be willing to drink ORS. However, some children who are significantly dehydrated do seem to refuse ORS or Pedialyte since they are either anorexic, too weak to drink, or are refusing because of behavioral reasons (i.e., "spoiled"). Children with mild dehydration can be placed on near normal diets (avoiding fat and excessive sugar), with good results in most instances.

Many textbooks will indicate that children with severe dehydration should be given immediate IV fluid boluses. While this is the standard practice in the U.S., it should be noted that in poor countries, many children with severe dehydration are successfully rehydrated using ORS. However, because severe dehydration is likely associated with a greater mortality risk than mild dehydration, it is reasonable to aggressively treat severe dehydration using IV fluids to reduce this risk. Even moderate dehydration could be treated using IV fluids since this reduces the risk of progression toward severe dehydration with its associated higher mortality risk. In the U.S. where IV fluid infusion resources are plentiful, there should be no hesitation to utilize IV fluids for severe dehydration.

For rapid IV rehydration, a fluid infusion utilizing normal saline (NS) or lactated Ringer's (LR) of 20 cc/kg is a common starting point. For severe dehydration, this should be given as a rapid bolus (over less than 10 minutes), but for mild dehydration this can be given over one hour. The term "isotonic" fluid is often used, but this is actually a misnomer. NS and LR are isotonic, but so is D5-1/4NS. All of these solutions have measured osmolarities of approximately 290. NS and LR behave very similarly since both have sodium concentrations similar to that of the serum. The major difference between NS/LR and D5-1/4NS is that NS/LR stays within the vasculature, while D5-1/4NS does not. Since fluid follows osmotic particles, the fluid volume will go, where the osmotic particles go. When NS/LR are used, the osmotic particles are largely sodium and chloride in concentrations very close to that of the circulating plasma. These ions stay within the circulating plasma and thus, the fluid volume expands the intravascular space preferentially. D5-1/4NS has a glucose concentration of 5000 mg/dL (D5W = 5% glucose = 5 grams/100cc). The serum concentration of glucose is only about 100 mg/dL. Thus, when D5-1/4NS is infused, the excess glucose is taken up by cells and converted to glycogen and the fluid volume leaves the intravascular space to enter the intracellular space. This might promote cellular edema under some circumstances, but at the very least, the fluid does not effectively expand the intravascular space. Thus, rather than use the term "isotonic IV fluids" to describe NS and LR, it would be more accurate to use the term "intravascular volume expanding IV fluids".

It should be noted that 20 cc/kg is actually a small volume. Take for example a 4 year child who weighs about 20 kg. 20 cc/kg results in a 400 cc fluid infusion. For mild dehydration this can be given over 1 hour so the IV rate would be 400 cc/hr for one hour. While this sounds like a very fast IV rate for a small child, this is actually a small volume. 20 cc/kg only replaces 2% of the body's weight, and thus it correctly for only 2% dehydration, which would be considered very mild and not generally in need of IV fluid rehydration. The 2% is determined by 400 cc divided by 20 kg (20,000 gms), or by 20 cc/kg (20 cc per 1000 cc = 2%). Another way to appreciate the truly small size of this fluid volume infusion is to equate this to soft drink cans, which are 12 ounce cans. Since 1 ounce equals 30 cc, a typical 12 ounce soft drink can contains 360 cc, which is similar to the 400 cc fluid infusion. One could say that we are giving a single can of IV fluid over an hour. Looking at it this way, most of us can see that this is not very much. Most 4 year olds can drink 3 or 4 soft drink cans on a hot day after a soccer game. Thus, 20 cc/kg fluid infusion volumes should almost always be repeated.

For severe dehydration in the range of 15%, the patient would actually need 150 cc/kg to fully replace the fluid deficit. For a patient with 5% dehydration, the patient would actually need 50 cc/kg to fully replace the fluid deficit. In addition to the deficit replacement, maintenance fluid needs must be added in.

Resuscitation of shock requires 20 cc/kg NS/LR as a rapid infusion and repeated until perfusion is restored. In most instances, fully rehydrating the patient very rapidly is not necessary and this may be harmful if excessive fluid shifts occur. Once satisfactory fluid resuscitation has stabilized the patient, continued rehydration and maintenance fluids can be administered more gradually.

Some patients with mild dehydration will prefer IV rehydration instead of oral rehydration. Although IV rehydration requires more resources and is more invasive, it has some definite advantages. Once the IV is in, fluid infusion is comfortable, rapid, and is not dependent on GI cooperation for absorption. Studies comparing IV and oral rehydration need to compare an "endpoint" to determine if the endpoint is better in one group or the other. Mortality is the most objective endpoint to measure. For mild dehydration, mortality risk is very low regardless of whether rehydration occurs orally or IV. IV rehydration results in rehydration certainty with minimal work by parents. Oral rehydration requires more work on the part of parents and some uncertainty exists as to whether it will be successful. Most parents bringing their child to an emergency department for IV hydration, have already attempted oral rehydration and they are not fully satisfied with the results. Even though IV rehydration may not be required, it is reasonable to offer it. Put yourself in the body of the child who is experiencing the vomiting and diarrhea. Imagine that you/he/she has vomited 8 times and has had 7 episodes of diarrhea beginning 8 hours ago. You have tried oral rehydration with ORS, but the vomiting and diarrhea have continued. Would you prefer to continue drinking ORS or would you prefer an IV fluid infusion, during which you would have to lie down and get some rest? At some point, many of us would prefer the IV route even though it is not required to avoid mortality. A rule of thumb is that an IV fluid infusion can be considered if V+D (vomiting and diarrhea episodes) is greater than or equal to 10. At this level, sufficient discomfort has been sustained by the patient and mild dehydration is likely. Most mildly dehydrated patients who are given 20 cc/kg per hour for 2 hours (total 40 cc/kg), feel much better with less nausea and fatigue. For such mild patients, they can usually be discharged from the emergency department to catch up on some rest. After a nap or overnight rest, oral rehydration attempts can resume, which are likely to be successful. Compare this to a similar oral rehydration patient, who is not permitted a nap and a period of bowel rest, and who must continue oral rehydration.

For inpatients who are hospitalized for IV rehydration, more time is available to gradually rehydrate the patient. Assuming that rapid IV fluid resuscitation has already taken place (or determined to be unnecessary), inpatient rehydration is a more complex calculation than emergency department rehydration. However, this knowledge is generally required for medical students and pediatric residents.

Fluid administration over a 24 hour period consists of deficit replacement plus maintenance administration. This is best described with the example presented in the case at the beginning of the chapter. A 12 month old male with vomiting and diarrhea is assessed to be 5% dehydrated by clinical criteria. His weight is 10 kg at presentation, but his pre-illness weight is not known. The patient's fluid deficit volume is 5% of 10 kg = 500 cc. The patient's maintenance fluid volume is 1000 cc. Fluid administration is generally broken up into 8 hour blocks for the next 24 hours. The maintenance fluid volume is administered evenly over the three 8 hour blocks. Half of the deficit volume is given in the first 8 hours, with one-fourth of the deficit volume given in the next two 8 hour blocks. This is diagrammed below:

	First 8 hours	Second 8 hours	Third 8 hours
Maintenance volume	1/3	1/3	1/3
Deficit volume	1/2	1/4	1/4

Fitting the clinical data for the patient's case results in the following volume calculations:

	24 hours	First 8 hours	Second 8 hours	Third 8 hours
Maintenance volume	1000 cc	333 cc	333 cc	333 cc
Deficit volume	500 cc	250 cc	125 cc	125 cc
Maintenance+Deficit	1500 cc	583 cc	458 cc	458 cc
IV rate		73 cc/hr	57 cc/hr	57 cc/hr

The IV rate is determined by the sum of the maintenance and deficit fluid volumes for the 8 hour block, divided by 8 hours as noted above. The next step is to determine the type of IV fluid to use (i.e., the optimal electrolyte content of the IV fluid). For maintenance IV fluids, Na is given as 3 mEq/100 cc of IV fluid, K is given as 2 mEq/100 cc of IV fluid. These electrolytes are replaced evenly over the three 8 hour blocks, as noted below (maintenance Na and K).

	24 hours	First 8 hours	Second 8 hours	Third 8 hours
Maintenance volume	1000 cc	333 cc	333 cc	333 cc
Maintenance Na	30 mEq	10 mEq	10 mEq	10 mEq
Maintenance K	20 mEq	7 mEq	7 mEq	7 mEq
Deficit volume	500 cc	250 cc	125 cc	125 cc
Deficit Na	??	??	??	??
Deficit K	??	??	??	??
Maintenance+Deficit	1500 cc	583 cc	458 cc	458 cc
IV rate		73 cc/hr	57 cc/hr	57 cc/hr

The deficit sodium and potassium are more difficult to determine. First of all it should be noted that if the onset of dehydration is rapid (e.g., over 12 hours), most of the fluid is lost from the extracellular space (intravascular and interstitial fluid). If the onset of dehydration is very gradual and prolonged (e.g., over 7 days), relatively more fluid is lost from the intracellular space as well, since the longer time interval permits fluids to shift from the ICF to the ECF space. The ECF (similar to plasma) has a high Na concentration (137 mEq/L) and a low K concentration (3.5 mEq/L). The ICF is the opposite of this to maintain a transmembrane gradient, such that the intracellular K concentration is about 140 mEq/L, while the intracellular Na concentration is close to zero. Deficit Na and K are calculated by the split of ECF and ICF. The ECF volume lost concomitantly loses 140 mEq/L of Na, while the ICF volume lost concomitantly loses 140 mEq/L of K. Short term dehydration results in mostly ECF loss (i.e., more Na and less K), while dehydration occurring over a prolonged period, results in more ICF loss (i.e., more K and less Na). The table below estimates the degree of ICF and ECF loss based on the duration of gastroenteritis symptoms.

Duration of symptoms (4):
- Less than 3 days: 80% ECF, 20% ICF
- 3 days or longer: 60% ECF, 40% ICF

Since our patient's dehydration occurred over one day, the ECF/ICF loss ratio is 80%/20%. Of the 500 cc fluid deficit, 400 cc is ECF loss, while 100 cc is ICF loss. ECF fluid loss contains 140 mEq Na per liter, while ICF fluid loss contains 140 mEq K per liter. Thus, the deficit Na lost is 140 X 0.4L = 56 mEq. The deficit K lost is 140 X 0.1L = 14. Deficit sodium is replaced in the same proportion as deficit fluid (i.e., 1/2, 1/4, 1/4) over the three 8 hour blocks. In contrast, only half of the deficit potassium is replaced and this is split evenly over the three 8 hour blocks (i.e., 1/6, 1/6, 1/6). This is a conservative approach since hyperkalemia due to a miscalculation could result in a life-threatening dysrhythmia. Another approach is to withhold all potassium until urine output is established and to begin potassium replacement at that time. The deficit and maintenance electrolytes can now be determined as in the table below:

	24 hours	First 8 hours	Second 8 hours	Third 8 hours
Maintenance volume	1000 cc	333 cc	333 cc	333 cc
Maintenance Na	30 mEq	10 mEq	10 mEq	10 mEq
Maintenance K	20 mEq	7 mEq	7 mEq	7 mEq
Deficit volume	500 cc	250 cc	125 cc	125 cc
Deficit Na (ECF 80%)	56 mEq	28 mEq	14 mEq	14 mEq
Deficit K (ICF 20%)	14 mEq	2.5 mEq	2.5 mEq	2.5 mEq
Maintenance+Deficit volume	1500 cc	583 cc	458 cc	458 cc
Maint+Def Na	86 mEq	38 mEq	24 mEq	24 mEq
Maint+Def K	34 mEq	9.5 mEq	9.5 mEq	9.5 mEq
IV rate		73 cc/hr	57 cc/hr	57 cc/hr
Na concentration		65 mEq/L	52 mEq/L	52 mEq/L
K concentration		16 mEq/L	21 mEq/L	21 mEq/L

For the first 8 hour period, the Na concentration must approximate 65 mEq/L, which somewhere between 1/2NS and 1/3NS. The IV order for the first 8 hour block could be "IV D5-1/2NS + 16 mEq KCl per liter run at 73 cc/hour for 8 hours." For the next 16 hours, the Na concentration must approximate 52 mEq/L which is approximately 1/3NS. The IV order for the next 16 hours should be "IV D5-1/3NS + 21 mEq KCl per liter run at 57 cc/hour for 16 hours".

Although this process is rather complex, a short cut exists. For 5% dehydration, which is the most common type of hospitalization, the fluid calculations can be approximated by D5-1/2NS + 20 mEq KCl per liter run at twice the maintenance rate for the first 8 hours, followed by D5-1/3NS + 20mEq KCl per liter run at 1.5 times the maintenance rate for the next 16 hours. For percentages other than 5%, this short cut will not work. For dehydration which occurs over more than 3 days, there is a greater loss of ICF (hence, more potassium loss) and relatively less ECF loss (hence, relatively less sodium loss), so the order can be modified to: D5-1/3+25 mEq KCl per liter run at 2 times maintenance for 8 hours, then 1.5 times maintenance for the next 16 hours.

Other factors can make these calculations even more complex. If the patient was given several rapid bolus infusions of NS in the preliminary resuscitation in the ED stabilizing the patient from 10% to 4% dehydration, a large amount of sodium was given initially. If the patient has hyponatremic or hypernatremic dehydration, then the sodium deficit will need to be recalculated. However in the acute resuscitation phase, it doesn't matter whether the patient is hyponatremic, normonatremic or hypernatremic, because the initial IV fluid indicated for resuscitation bolus infusions is NS or LR. The correction of hyponatremia, hypernatremia, hypokalemia and hyperkalemia is beyond the scope of this chapter. However, most cases of mild sodium and potassium imbalance, will eventually correct with most methods of calculating fluid replacement, as long as the kidneys remain functional to ultimately correct the imbalance. Correcting extreme deviations of sodium and potassium should be done with caution. Rapid electrolyte correction can result in cellular damage due to excessive fluid shifts. The use of 3% sodium chloride solution (more than 3 times the osmolarity of NS) should be used with extreme caution since this can cause severe hypernatremia in a short period of time. Administering potassium IV to correct hypokalemia is also dangerous, especially for infants since a small dose of IV potassium can easily make the patient critically hyperkalemic. A general recommendation is that, if the patient is stable, it is best to correct the electrolyte imbalance slowly.

Every day basic numbers to know (and memorize):
Maintenance fluid volume calculation: 100, 50, 20
Maintenance electrolytes: 3meq Na/100cc, 2meq K/100 cc
Volume expanding bolus (NS or LR): 20 cc/kg NS
Normal osmolarity 290 mosm/liter
30 cc = 1 ounce.

Questions:

1. Which of the following sets of signs and symptoms are most consistent with 5% dehydration?
    a. oliguria, tears with crying, less active than usual, normal skin turgor, moist oral mucosa.
    b. oliguria, no tears with crying, less active than usual, sticky oral mucosa, normal or slightly diminished skin turgor.
    c. oliguria, no tears with crying, sunken eyes, soft doughy skin (diminished skin turgor) without tenting.
    d. oliguria, sunken eyes, tenting, tachycardia, hypotension.

2. Which of the following sets of signs and symptoms are most consistent with 10% dehydration?
    a. oliguria, tears with crying, less active than usual, normal skin turgor, moist oral mucosa.
    b. oliguria, no tears with crying, less active than usual, sticky oral mucosa, normal or slightly diminished skin turgor.
    c. oliguria, no tears with crying, sunken eyes, soft doughy skin (diminished skin turgor) without tenting.
    d. oliguria, sunken eyes, tenting, tachycardia, hypotension.

3. Calculate the maintenance IV fluid and rate for a 4 kg infant and for a 25 kg 6 year old.

4. Estimate the concentration of sodium in NS, 1/2NS, 1/3NS and 1/4NS.

5. The resident writes an order for "isotonic" IV fluid to be bolused immediately for a patient with shock and severe dehydration. You look at all the IV fluid bags and notice that NS has an osmolarity of 310, LR has an osmolarity of 275, and D5-1/4NS has an osmolarity of 320. You grab a bag of D5-1/4NS. The resident tells you to get normal saline instead. Why is D5-1/4NS inappropriate even though it is "isotonic"?

6. You calculate the 24 hour maintenance volume for a 3 kg child with severe neurologic dysfunction. His maintenance volume is 300 cc/day. He is currently being fed infant formula via a nasogastric tube at 3 ounces every 3 hours. You do a calculation and notice that he is getting 720 cc/day which is more than twice his maintenance volume. Why isn't this child in congestive heart failure from fluid overload? Explain what maintenance means.

7. You are working as a volunteer physician in a refugee camp of a poor country. The clinic staff has a total of 5 IV sets and there are over 100 children presenting to your clinic with diarrhea and dehydration today. You are seeing a 10 month old infant who is thin and appears to be about 10% dehydrated. Should you use one of the IV sets, or should you implement oral rehydration? A company has donated 1000 liters of Pedialyte which are available for use. What is your rehydration plan for this patient?

8. Calculate an IV rehydration to be administered over 24 hours for a 16 kg child who is 7% dehydration from vomiting and diarrhea which has taken place over 4 days. Start by filling in the table below:

	24 hours	First 8 hours	Second 8 hours	Third 8 hours
Maintenance volume	_____cc	_____cc	_____cc	_____cc
Maintenance Na	_____mEq	_____mEq	_____mEq	_____mEq
Maintenance K	_____mEq	_____mEq	_____mEq	_____mEq
Deficit volume	_____cc	_____cc	_____cc	_____cc
Deficit Na	_____mEq	_____mEq	_____mEq	_____mEq
Deficit K	_____mEq	_____mEq	_____mEq	_____mEq
Maintenance+Deficit volume	_____cc	_____cc	_____cc	_____cc
Maint+Def Na	_____mEq	_____mEq	_____mEq	_____mEq
Maint+Def K	_____mEq	_____mEq	_____mEq	_____mEq
IV rate		_____cc/hr	_____cc/hr	_____cc/hr
Na concentration		____mEq/L	____mEq/L	____mEq/L
K concentration		____mEq/L	____mEq/L	____mEq/L
Type of IV fluid		_____	_____	_____

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Answers to questions

1. b
2. c
3. 4kg: 4 X 100 = 400 cc over 24 hours. 3 mEq Na per 100 cc, 2 mEq K per 100 cc. D5-1/4NS + 20 mEq KCl per liter run at 17 cc/hour. 25 kg: 1500 + 5 X 20 = 1600 cc over 24 hours. Maintenance electrolytes are the same. D5-1/4NS + 20 mEq KCl per liter run at 67 cc/hour.
4. Since normal osmolarity is about 300, the Na concentration in NS must be about half that (since Na and Cl ions make up the total osmolarity), which is 150 mEq/L. 1/2NS is half that (75 mEq/L), 1/3NS is 50 mEq/L and 1/4NS is 38 mEq/L.
5. An intravascular volume expanding fluid is required to resuscitate severe dehydration and hypovolemic shock. D5-1/4NS is not an intravascular volume expanded (see text). NS and LR are intravascular volume expanders. The resident should not have used the term "isotonic" since what he/she really meant, was to administer an intravascular volume expanding IV solution.
6. The patient has normal kidneys, which will regulate his overall fluid status. Even normal infants drink about 250 cc/kg (about 2.5 times maintenance), which is why they use a lot of diapers. Since formula is only 2/3 of a calorie per cc, he needs more than maintenance to reach maintenance caloric intake. His excess fluid volume will be urinated out. Maintenance fluid volume is the volume which results in minimum work for the kidney. If less than maintenance fluid is taken in, the kidney must work (consume energy) to retain fluid. If more than maintenance fluid is taken in, the kidney must work to excrete excess fluid. Kidney energy consumption (work) is minimized at some point between these two extremes and this is the "maintenance volume". Patients receiving fluid volumes less than or greater than maintenance will not likely develop fluid balance problems as long as their kidneys are functioning normally. However, if they are very ill, it would be best to minimize renal stress by optimizing their fluid balance.
7. Oral rehydration with WHO ORS should be implemented immediately. Pedialyte is for maintenance fluid, is suboptimal for rehydration and is only useful for children with mild dehydration. This child is not ill enough to utilize one of the 5 IV sets available. According to studies, the mortality rate for oral rehydration and IV rehydration are the same for this type of dehydration.

8. 24 hour maintenance volume is 1300 cc. This is split up into three even 8 hour blocks. Maintenance electrolytes are 3 mEq Na and 2 mEq K per 100 cc. Deficit volume is 1120 cc (7% of 16 kg), half of which is given in the first 8 hour block with the other half distributed over the next two 8 hour blocks (1/4 for each 8 hour block). Since dehydration has occurred over a 4 day period, 60% of the deficit comes from the ECF (672 cc) and 40% comes from the ICF (448 cc). Thus, the sodium replacement for ECF fluid is 140 mEq per liter and the potassium replacement for ICF is 140 mEq per liter. The Na deficit is replaced as the deficit fluid is replaced over the next three 8 hour blocks (1/2 + 1/4 + 1/4). Half of the K deficit is replaced distributed evenly over the three 8 hours blocks (1/6 + 1/6 + 1/6). The results of these calculations are shown below:

Weight 16 kg 7% dehydration	24 hours	First 8 hours	Second 8 hours	Third 8 hours
Maintenance volume	1300 cc	433 cc	433 cc	433 cc
Maintenance Na	39 mEq	13 mEq	13 mEq	13 mEq
Maintenance K	26 mEq	9 mEq	9 mEq	9 mEq
Deficit volume	1120 cc	560 cc	280 cc	280 cc
Deficit Na (60%)	94 mEq	47 mEq	24 mEq	24 mEq
Deficit K (40%)	63 mEq	10 mEq	10 mEq	10 mEq
Maintenance+Deficit volume	2420 cc	993 cc	713 cc	713 cc
Maint+Def Na	133 mEq	60 mEq	37 mEq	37 mEq
Maint+Def K	89 mEq	19 mEq	19 mEq	19 mEq
IV rate		124 cc/hr	89 cc/hr	89 cc/hr
Na concentration		60 mEq/L	52 mEq/L	52 mEq/L
K concentration		19 mEq/L	27 mEq/L	27 mEq/L

D5-1/3NS+19 mEq KCl per liter run at 124 cc/hour for 8 hours, then D5-1/3NS+27 mEq KCl per liter run at 89 cc/hour for 16 hours. The KCl should actually be approximated to 20 mEq/L for the first 8 hours, then 25 mEq/L for the next 16 hours. This would make it easier for the nursing staff to carry out the order.

Chapter II.5. Failure to Thrive
Anthony P. S. Guerrero, MD

This is a 12 month old female who presents for a well child check. Within the past 4 months, her weight has fallen from the 25th percentile to significantly less than the 5th percentile. Her height has dropped from the 10th percentile to slightly less than the 5th percentile, while her head circumference has remained at about the 25th percentile. Her language, motor, cognitive, and social development are normal. She seems to eat appropriate foods for her age, but the her mother notes that she tends to be restless and fidgety while eating, and that she does not like the texture of certain foods, often leading to parental frustration at mealtimes. Her stools tend to be frequent, with particles of food seen. Urine is normal. There are no symptoms of respiratory or neurological disease, and her review of systems is otherwise negative.

Her past medical history is entirely unremarkable. She was born at term, weighing 3.0 kg (6 pounds, 10 ounces), without any perinatal complications. Her family history is negative for any endocrinopathies or chronic illnesses. Mother is 155 cm (5 feet, 1 inch) 61 inches tall, and father is 168 cm (5 feet, 6 inches). Mother experienced menarche at age 12.5 years and recalls that there were other children in the family who were deemed small as young children but who caught up later in childhood. Mother describes a history of increased sadness and worry since her child was born. Parents are married, and there is no history of abuse or violence in the household.

Exam: Vital signs, including blood pressure, are normal. Weight 7 kg (< 5th percentile), height 70 cm (5th percentile), head circumference 45.5 cm (50th percentile). She is alert and interactive, and appears to relate well with her mother. Her anterior fontanelle is still open, roughly 2 cm. Two teeth (one just emerging) are present. Thyroid, lymph nodes, heart, lungs, abdomen, genitalia, nervous system, and skin are all normal.

Laboratory studies: CBC, chemistry panel, lead level, TSH, urinalysis, PPD, and stool studies, including ova and parasites all normal. Bone age is consistent with skeletal maturity of an 8 month old infant.

Formulation: Failure to thrive, with components of genetic short stature with a family history of constitutional growth delay. Parental anxiety, active temperament, and oral/tactile sensitivity may lead to feeding difficulties.

Clinical course: The primary care physician sees the child and family every few months for support, ongoing education, and coordination of services. A dietitian assists in devising an enhanced calorie diet for the child. An occupational therapist offers suggestions for reducing sensitivity to certain food textures. A psychiatrist provides treatment for what is felt to be mild post-partum depression in the mother. Two years later, the child is at the 5th percentile for both height and weight and is otherwise doing well.

Failure to thrive (FTT) is a clinical sign (rather than a specific diagnosis) that describes inadequate growth and is defined as (1) a child younger than 2 years of age whose: 1) weight is below the 3rd or 5th percentile for age on more than one determination; 2) weight is less than 80% of ideal weight (i.e., 0.8 times ideal weight) for age; or 3) weight crosses two major percentile curves on a standardized growth grid (2). FTT is a relatively common problem that may be seen in 10% of children in a rural primary care setting during the first year of life and may account for 1% to 5% of all referrals to children's hospitals and tertiary care settings (3).

The etiologies of FTT are diverse. To arrive at a list of differential diagnoses (which essentially can include most pediatric illnesses), one can think critically about the disease conditions that may interfere with any of the steps in the mechanisms leading to normal growth.

Feeding etiologies include food unavailability, neglect, improper feeding technique, appetite loss, food refusal, and neurologic conditions with impaired swallowing. Other etiologies may include intestinal disease conditions or anatomic abnormalities, endocrinopathies, chronic or prolonged infection, malignancies, other chronic diseases, toxic substances and metabolic derangements.

The patterns of increase in weight, height, and head circumference over time are important to note. Weight reduction out of proportion to height and head circumference may result from malnutrition. Weight reduction in proportion to height reduction but with sparing of head circumference may result from structural dystrophies, genetic short stature, and other endocrinopathies. Global weight, height, and head circumference reduction may result from central nervous system defects or intrauterine growth retardation. The timing of the reduction in weight may also be important to note, as a fairly sudden reduction in velocity of weight gain may reflect either the development of a chronic illness or an adverse social circumstance. Other specific signs and symptoms associated with FTT will vary according to the specific etiology (4).

Because the differential diagnosis can be so broad, a thorough history, growth chart review, and physical examination are key in the evaluation of FTT. Mindful of the mechanisms underlying normal and abnormal growth, one should elicit: a thorough feeding history (beyond the usual "diet" history), a comprehensive review of systems (which often gets dismissed in favor of "as per HPI"), a developmental and psychosocial history, and a history of family members' growth, development, and medical illnesses. It is potentially useful to determine the mid-parental height. For boys: father's height + mother's height + 13 cm]/2. For girls: father's height - 13 cm + mother's height]/2. Plot this on the growth grid for 2 to 18 year olds, estimate the percentile of the child's predicted height, and compare this to the current growth percentiles (as was done in the case above). However, parental short stature does not automatically imply genetic short stature, as either of the parents could have been adversely affected by malnutrition and/or chronic illness. Physical exam should include all vital signs and organ systems and should note the child's level of physical development (e.g., fontanelle size, dentition, etc.).

In the child with a "normal" history and physical examination, there is no clear consensus on what should constitute a "screening" laboratory evaluation, and it is possible that certain laboratory tests may have more value for reassurance rather than substantial diagnostic yield. However, it may be reasonable to consider a complete blood count, basic chemistries, urinalysis, and tuberculin test (1). Laboratory tests that would be appropriate for routine well child care (e.g., lead level) are also reasonable. Further laboratory tests should be guided by specific findings on history and physical examination. In the case above, stool studies were obtained because of the possibly abnormal stools, and a TSH and bone age were obtained because of the possibly delayed skeletal growth.

Management of FTT is based upon a sound understanding of the underlying etiologies. Traditionally, FTT has been categorized into "organic" and "non-organic" etiologies, but recently, it has been recognized that nearly every case of FTT may have both "organic" components (e.g., cyanotic heart disease) and "non-organic" components (e.g., the stressful feeding interactions taking place around a fragile, fussy child), thereby challenging the clinician to approach management in a comprehensive manner. For the case described above, there are multiple interactions between the various factors: for example, the perception of an "abnormal" child (being small for age; albeit with a strong constitutional element) could increase parental anxiety (compounding the depressive symptoms) and could render the parent-child interactions (already challenged by the child's active temperament and sensitivity to food textures) even more difficult. Hence, ongoing support and education from the primary care physician and referrals to psychiatry and occupational therapy become important components of the treatment plan.

An important priority is the establishment and maintenance of adequate nutrition, and caloric intake should be determined based upon child's age, need for "catch up" growth, and (if applicable) increased needs in illness. Creative methods, including more frequent meals and snacks, high calorie foods (e.g., peanut butter, margarine), and nutritional supplementation (e.g., PediaSure) can be employed to augment the child's natural intake. If these methods are unsuccessful after a reasonable trial, supplementation via nasogastric feeds may be indicated.

In the past, hospitalization was felt to be important in differentiating between "organic" and "non-organic" etiologies, as it was believed that the former would not gain weight in the hospital, while the latter would. However, hospitalization may not necessarily distinguish the two, as children with "organic" FTT may, in fact, gain weight with around the clock feeding in the hospital, while certain children with "non-organic" FTT (e.g., with conditions involving an anxious temperament and/or difficulty adjusting to new environments) may become even less likely to feed in a hospital setting. On the other hand, hospitalization must be considered in cases where a child is at risk of serious medical morbidity as a result of either malnutrition or the condition underlying the FTT or at risk of neglect or abuse.

Children with FTT have been found to be at higher risk for adverse cognitive and other developmental/behavioral outcomes, although it is not clear the extent to which these are related to the medical conditions underlying the FTT, subtle neurological dysfunctions which manifested themselves pre-morbidly as feeding and interactional difficulties (hence FTT), or ongoing psychosocial adversity. Nevertheless, because of the known importance of good nutrition for brain development during the first few years of life, it is highly important to identify any potential growth disturbances and suboptimal feeding practices during routine well child care and to expeditiously manage FTT.

Questions (true or false):

1. "Organic" and "non-organic" FTT are clearly defined conditions which enable pediatricians to focus treatment on "organic" cases.
2. Hospitalization is indicated when a child is at risk of serious medical morbidity or abuse/neglect.
3. In addition, all children with FTT should be hospitalized to distinguish between "organic" and "non-organic" etiologies.
4. Blood pressure is useful in evaluating young children with FTT.
5. If both parents are of short stature, then the child must have genetic short stature.
6. History, growth chart review, and physical are key in the evaluation of FTT.
7. In evaluating a child with FTT, it may be important to elicit any history of excessive thirst, increased urination, and family members with renal disease.

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Answers to questions
1.F, 2.T, 3.F, 4.T (can help detect renal disorders), 5.F, 6.T, 7.T

Chapter II.6. Malnutrition and Vitamin Deficiencies
Adeline Winkes, MD

An 18 month old boy is brought to the emergency room by police for evaluation. He and his siblings were all removed from their home earlier in the day, after a neighbor's complaint. There are no parents or guardians present to give a history, although the police officer comments that the mother is thought to be an injection drug user. The 12 year old sister, who seems to be the primary caregiver, is worried that the toddler is sick, stating that "he's gotten really skinny" and he "keeps a cold," with constant rhinorrhea and cough. She is unsure if he has seen a doctor, but thinks that he "got all his baby shots".

Diet history is revealing: meals are generally prepared by the 12 year old and 10 year old siblings, and consist of packaged macaroni and cheese, canned spaghetti or noodles, peanut butter and jelly sandwiches, and occasionally fast food drive-ins. The older kids usually drink juice and sodas, though the toddler also drinks some milk.

On exam, the toddler is anxious, clinging to his older sister. He appears thin, with a large head and subcutaneous wasting. Vital signs are appropriate for age. Weight is 9 kg (<3rd percentile); height is 72 cm (<3rd percentile); head circumference is 47 cm (10th percentile). Exam is significant for subcutaneous wasting, sparse hair, dry skin, and a scaling rash in the diaper area. There are no overt signs of trauma, and no focal neurologic deficits.

Laboratory evaluation is significant for a microcytic anemia and a decrease in serum albumin. The toddler is admitted to the hospital for protection, and monitoring during the refeeding process, which proceeds without incident. With concern for infectious risk factors, an HIV test is ordered - which is positive. CD4 count is 1500. Antiretroviral therapy is instituted, with good immunologic response. With the provision of sufficient calories and protein in the diet, weight gain begins to improve.

Protein-energy malnutrition unfortunately remains a significant problem, both in developing countries, and in poverty-stricken areas of the industrialized world. Children with chronic or acute illness are at particular risk, particularly those with acute illnesses including: burns, sepsis, head injury, trauma, malabsorptive disorders, chronic liver, renal, or cardiac diseases, cancers, and HIV. Protein-energy malnutrition may present as the classic syndromes of marasmus and kwashiorkor, or more commonly, with overlap between the two.

Marasmus (1,2) is a classic description of a deficiency in the somatic protein compartment, resulting from primarily a caloric or energy deficiency, and leading to generalized muscular wasting and the loss of subcutaneous fat. The skin appears dry, loose, and wrinkled. Hair may become thin, sparse, and brittle. Hypothermia, bradycardia, hypotension, and hypoglycemia may occur. The visceral protein compartment (discussed below) is relatively spared. As a result, serum albumin measurements are generally normal, though anemia and evidence of vitamin deficiencies are common. There may be a coexisting T cell-mediated immune deficiency.

Kwashiorkor (1,2), in contrast, is a deficiency of the visceral protein compartment, resulting from a protein deficiency (in excess of the caloric deficiency), and leading to edema, dermatoses (including hyperkeratosis, dyspigmentation), dry, brittle, and sometimes red or yellowish hair (if alternating periods of protein deprivation, they may have alternating bands of hair texture = flag sign), hepatomegaly (fatty infiltration), protruding abdomen, and impairment in T cell-mediated immune deficiency. Risk of secondary infections is therefore increased. Laboratory abnormalities may include a low serum albumin, mineral deficiencies (iron, zinc, copper), and elevations of blood glucose, white blood cell count, urine nitrogen, and serum ferritin (as an acute phase reactant even if they are iron deficient). Other acute phase reactants may also be increased (3). Kwashiorkor has been known to occur in toddlers weaned to a protein deficient diet (white rice, yams, cassava-a Latin American staple root otherwise known as manioc or yucca), or in chronically ill or hospitalized patients, in the industrialized world. If kwashiorkor develops in patients with acute illness, such as burns, sepsis, or trauma, it will not resolve entirely until the underlying illness resolves.

Marasmus and kwashiorkor are at two ends of a spectrum of protein-energy malnutrition. In the industrialized world, a mixed picture is most common, often in the setting of chronic disease (perhaps impairing protein absorption), or acute illness (leading to an increase in the basal metabolic rate). Those who live in poverty are at increased risk, as are infants, adolescents, pregnant women, alcoholics, and patients with eating disorders. Assessment should include a careful diet history, comprehensive medical history and physical exam, with the goal of eliciting underlying medical problems. Particular attention should be paid to identifying possible co-morbid conditions, and likely concurrent vitamin deficiencies. Growth measurements should include weight, height and head circumference with adjustments for age, weight for height comparisons, and a body mass index (kg/m2) calculation for children older than 2 years of age. Children whose weights are less than 80% of expected (ideal body weight estimated by tracking growth over time, as well as weight-for-height for infants or body mass index measurements for older children) are considered malnourished. Children with marasmus generally fall as low as 60% of expected. Children with kwashiorkor (and concurrent edema) tend to fall between 60-80% of expected (2). A body mass index measurement of less than 18.5 is considered underweight (3). Treatment consists of the provision of adequate calories and protein to meet individual needs, and treatment of any underlying disease states. In severe malnutrition, close monitoring may be necessary to prevent complications such as refeeding syndrome (severe hypophosphatemia and consequences thereof, as complication of nutritional rehabilitation in severely malnourished patients) (1).

Vitamin deficiencies can be divided into deficiencies of fat-soluble vitamins (ADEK) and deficiencies of water-soluble vitamins, including vitamins B, C, folate, and niacin.

Vitamin A (2) (retinol, retinol ester, retinal, retinoic acid) is found in both plant and animal sources. Animal sources include liver, fish, eggs, milk, and butter. Plant sources include green leafy vegetables and some of the yellow vegetables, such as carrots and squash, as well. These also provide provitamins such as betacarotene, which may be further metabolized to vitamin A. Vitamin A functions as an essential component of visual pigments, and has a role in the maintenance of mucus-secreting epithelia, which may contribute to its role in resisting infection. Deficiency syndromes are therefore notable for: impaired vision, particularly at night, xerophthalmia (in which normal epithelium is replaced by keratinized epithelium), squamous metaplasia of the airways leading to secondary pulmonary infections, renal or urinary bladder stones, and immunodeficiencies. Vitamin A has also been studied as a supplement for use during acute infections, in the developing world. The mechanism is unclear, but it appears to be useful in particular disease states, with or without underlying vitamin A deficiency. This has led to a Red Book recommendation for vitamin A supplementation in some patients with measles (4,5).

Vitamin D (2) is found in two precursor forms: 7-dehydrocholesterol (provitamin D3) in the skin, and ergosterol in plants. It is synthesized endogenously from its precursor in the skin, and found in dietary sources such as: deep-sea fish, plants, and grains. It serves in the maintenance of appropriate serum calcium and phosphorus levels, through the regulation of intestinal absorption of calcium/phosphorus, the PTH-mediated mobilization of calcium from bone, and the PTH-mediated stimulation of calcium reabsorption in the distal renal tubules. Deficiency states are referred to as rickets in children, or osteomalacia in adults. Populations at risk for deficiency states are usually marked by limited sun exposure, and therefore inadequate endogenous synthesis, as well as a diet limited in vitamin D. The classic syndrome of rickets is marked by: craniotabes, rachitic rosary, wrist thickening, pigeon breast deformity, Harrison groove, flaring epiphyses, and bowing of the legs. This might be seen in breast-fed infants or toddlers, whose mothers are not supplementing with vitamin D. These children would likely also have sun exposure that was limited in some way, such as during the winter in northern latitudes.

Vitamin E (2) consists of the group of tocopherols and tocotrienols, of which alpha-tocopherol is the most common. Sources include: vegetables, grains, nuts, dairy, fish, and meats. It serves as an antioxidant, and is especially important in the nervous system and mature red blood cells. Deficiency syndromes of vitamin E are extremely uncommon, and are usually seen only in patients with fat malabsorption or other complicating chronic medical conditions. Deficiency syndromes are marked by posterior column/dorsal root ganglion-related signs, including: absent tendon reflexes, ataxia, loss of position and vibration sense, loss of pain sensations. Ophthalmoplegia may occur. Anemia has been reported in premature babies.

Vitamin K deficiency (2) may produce hemorrhagic disease of the newborn, which is fortunately rare, as vitamin K prophylaxis at birth has become routine. Vitamin K is derived from vegetables and by synthesis by intestinal bacteria in the lower ileum and colon. Absorption of vitamin K in the small intestine is dependent on bile salts. After absorption, transport occurs to the liver. It is converted in the liver to the hydroquinone form, which acts as a cofactor in carboxylase reactions, including the carboxylation of glutamic acid residues, in the formation of factors II, VII, IX, X, protein C and protein S (6). It is readily recycled in a healthy liver, and is widely available in the diet. Deficiency usually occurs, therefore, only in high risk populations. All infants are at some risk for vitamin K deficiency, as: 1) liver reserves are limited in the neonatal period, 2) the bacterial flora which produce vitamin K have not yet been established, and 3) the level of vitamin K in breast milk is low. A 3% prevalence of vitamin K dependent bleeds in neonates (who have not received prophylaxis) has been estimated (2). By 1-2 weeks of age, the developing bacterial flora provide sufficient vitamin K for normal term infants' needs. Premature infants, for several reasons, may have persistent need for increased supplementation. In older children and adults, vitamin K deficiency may occur in those with fat malabsorption syndromes (biliary tract disease, short gut syndrome) and advanced liver disease, as hepatocyte dysfunction interferes with synthesis of vitamin-K-dependent coagulation factors, even in the presence of vitamin K levels considered sufficient in other settings (2,7). Vitamin K supplementation (in addition to other fat-soluble vitamins) is therefore recommended for patients with fat malabsorption, cholestasis, and advanced liver disease (7).

Vitamin B1 (2) (active coenzyme thiamine pyrophosphate) is found in a wide variety of dietary sources, with the notable exception of refined foods, such as polished rice, white flour, and white sugar. It participates in the regulation of ATP, as a cofactor in the pentose phosphate pathway. It also has a role in maintaining membranes and conduction pathways of the peripheral nerves. Populations that are particularly at risk for vitamin B1 deficiency include those whose diets are high in refined foods, such as polished rice, and those with alcoholism. Several clinical deficiency states have been described, including: dry beriberi (polyneuropathy with toedrop/footdrop/wristdrop), wet beriberi (cardiovascular manifestations including peripheral vasodilation and high output cardiac failure), and Wernicke-Korsakoff syndrome (encephalopathy, with ataxia and psychosis, including retrograde amnesia, confabulation).

Vitamin B2 (2), or riboflavin, is derived from meat, diary, and vegetable sources. It is involved in oxidation-reduction reactions, and is incorporated into mitochondrial enzymes. The clinical deficiency syndrome consists of: cheilosis (fissures in the lips), glossitis, keratitis/corneal ulceration, and a greasy scaling dermatitis over the nasolabial folds, progressing to a butterfly distribution.

Niacin (2), or nicotinic acid and its derivatives, is endogenously synthesized from tryptophan, and exogenously derived from grains (in some grains, such as corn, it exists only in the bound form and is therefore not absorbable), legumes, seed oils, and meats. It is a component of NAD and NADP, and acts as a coenzyme for dehydrogenation reactions, especially those in the hexose monophosphate shunt, in glucose metabolism. Populations at particular risk for niacin deficiency include: those with chronic diarrhea, those with protein-deficient diets, and those taking isoniazid and 6-mercaptopurine. The clinical deficiency syndrome of pellagra consists of dermatitis, diarrhea, and dementia.

Vitamin B6 (2), or pyridoxine and the phosphorylated forms thereof, is found in almost all foods, though they may be lost after processing (such as dried milk preparations). It acts as a cofactor for a large number of enzymes, including the transaminases, carboxylases, deaminases, in lipid metabolism, amino acid metabolism, and immune responses. An overt deficiency of B6 is rare, but the subclinical deficiency state is common, particularly in those being treated with pyridoxine antagonists, such as isoniazid, estrogens, penicillamines, and acetaldehyde (ETOH met). There is an increased demand for vitamin B6 during pregnancy. The clinical deficiency syndrome is similar to that seen in riboflavin or niacin deficiency: seborrheic dermatitis, cheilosis, glossitis, peripheral neuropathy, and sometimes seizures. Pyridoxine is used as a therapeutic reversal agent in pyridoxine-dependent seizures and in the acute management of INH overdose.

Vitamin B12 (2) is derived from animal sources (meats, milk, eggs), and is absorbed in the distal ileum, only after forming a complex with intrinsic factor (produced by gastric parietal cells). It is then transported by transcobalamin. Adequate B12 is required for normal folate metabolism, and also for DNA synthesis and the maintenance of myelinization of spinal cord tracts. Populations at particular risk for deficiency include: neonates (if the maternal diet is deficient), those with insufficient production of intrinsic factor (juvenile pernicious anemia), and those in whom the distal ileum has been surgically removed. The clinical deficiency state may include:

megaloblastic anemia, leukopenia, thrombocytopenia, mild jaundice, and neurologic signs, such as posterior/lateral column demyelination, paresthesias, sensory deficits, loss of deep tendon reflexes, confusion, and memory deficits.

Folate (2) is derived from a variety of sources (whole wheat flour, beans, nuts, liver, green leafy vegetables), but is quite heat labile, and easily destroyed by cooking or processing raw foods. It acts as an essential cofactor in nucleic acid synthesis. Populations at particular risk include: 1.) fetuses with rapidly dividing cells (in whom an association with neural tube defects has been noted. Hence the recommendation for early supplementation, for all women of childbearing age); 2.) those on oral contraceptives, antiepileptics, ETOH, or with heavy cigarette use (decreases absorption); or 3.) those with intestinal malabsorption or metastatic disease. It is notable that adequate B12 is required for folate metabolism, leading commonly to concurrent deficiencies. Deficiency in folate alone will produce a megaloblastic anemia. In a deficiency of B12, supplementation of folate will reverse the megaloblastic anemia, but it will not reverse the neuropathic consequences of B12 deficiency.

Vitamin C (2), or ascorbic acid, is found in milk, liver, fish, fruits, and vegetables. It is involved in the activation of prolyl and lysyl hydroxylases from inactive precursors, therefore facilitating the hydroxylation of procollagen. Populations at particular risk for vitamin C include those with marginal or erratic diets (the classic example is of malnourished sailors without fresh vegetables), dialysis patients, or infants on processed milk only. The clinical spectrum of vitamin C deficiency encompasses bone disease (in growing children), hemorrhagic disease (skin, mucosal, and subperiosteal bleeds, bleeds into joint spaces), impaired wound healing, and anemia.

Questions

1. Name the classic syndrome:
   A. Toddler with edema, hepatomegaly, protruding abdomen, alternating bands of light and dark hair, dry skin, and lethargy.
   B. Cachectic infant with subcutaneous fat wasting, loose dry skin, brittle hair.

2. True/False: Serum albumin is usually decreased in kwashiorkor, or severe malnutrition affecting the visceral protein compartment.

3. True/False: Hemorrhagic disease of the newborn can be prevented with vitamin K prophylaxis (1 mg IM x 1) at birth.

4. Vitamin K is an important cofactor in the activation of which of the following coagulation factors:
   a. factor VIII
   b. factor X
   c. protein S
   d. von Willebrand's protein
   e. factor IX

5. True/False: Vitamin D, in response to serum hypocalcemia, regulates the mobilization of serum calcium through three mechanisms: increased intestinal absorption of Ca and Phos, mobilization of Ca from bone, and increased reabsorption of Ca from the distal renal tubules.

6. The three D's of pellagra are:
   a. diarrhea
   b. dementia
   c. deafness
   d. dermatitis
   e. dissociation

7. Cheilosis and glossitis are features of:
   a. vitamin A deficiency
   b. riboflavin (B2) deficiency
   c. vitamin C deficiency
   d. pyridoxine (B6) deficiency
   e. vitamin E deficiency

8. True/False: Both folate and B12 deficiency produce a megaloblastic anemia. In addition, patients with B12 deficiency may exhibit posterior column defects, such as: paresthesias, sensory deficits, loss deep tendon reflexes, as well as confusion and memory deficits.

9. The features of scurvy, or vitamin C deficiency, include:
   a. bone disease in growing children
   b. hemorrhagic disease, including mucosal involvement, subperiosteal bleeds, and bleeding into joint spaces
   c. cheilosis, glossitis
   d. impaired wound healing
   e. anemia

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Answers to Questions

1. A. kwashiorkor. B. marasmus
2. True
3. True
4. b, c, e
5. True
6. a, b, d
7. b, d
8. True
9. a, b, d, e

Chapter III.1. Routine Newborn Care
Joan Ceccarelli Meister, MD

This is a 3640 gram newborn male infant born at 39 weeks gestation via normal spontaneous vaginal delivery (NSVD) to a 17 year old G3P0 mother who is O+, VDRL NR, Hepatitis B surface antigen (HBsAg) positive, rubella immune, group B streptococcus (GBS) negative, and HIV negative . Artificial rupture of membranes (AROM) occurred 18 hours prior to delivery with clear fluid. Apgar scores were 8 and 9 at 1 and 5 minutes respectively.

Maternal history is remarkable for 1 prenatal visit 1 month ago. An ultrasound performed at that time was consistent with 34 weeks gestation. Toxicology screening at that visit and on admission were negative. Mother is reportedly healthy, with no chronic medical problems and no significant family history. She reports no difficulty during the pregnancy. She denies alcohol, cigarette, medication or drug use. Social history reveals that the mother's support system includes the father of the baby (FOB) and both maternal and paternal grandparents.

Exam: VS T 37.0 rectal, P 145, R48, BP 49/35. Weight 3640 grams (8 pounds) (75th%), 51 cm (20 inches) (75th%), head circumference 34 cm (13.5 inches) (50th%). This infant is term in appearance, pink and active. Anterior fontanelle is soft and flat. Caput succedaneum is present. Corneas are clear. Ears are normally placed. Nares are patent. Oral mucosa is pink and the palate is intact. Neck is supple without masses. Clavicles are intact. His chest is symmetric and mature breast buds are present. Lungs are clear with equal aeration. Heart is regular with no murmurs heard. Abdomen is flat and soft with no masses. Three vessels are visible within the umbilical cord. Femoral and brachial pulses are symmetric and 2+. Hips demonstrate full range of motion, no tightness, no clicks. Ortolani and Barlow signs are negative. Perineal creases are symmetric. Anus is patent. Male genitalia are normal, with both testes descended. His skin is pink with a few facial petechiae. He moves all extremities well. His Moro reflex is intact. His grasp response is symmetrical. His suck reflex is strong.

By 7 hours of age, he has passed meconium once, has had no urine output, and has nippled 15 cc of infant formula from a bottle. His mother does not want to breastfeed because she says she has no milk and will be returning to school soon. Besides, she read that formula makes your baby grow just as well as breast milk. During a discussion between one of the pediatric residents and the mother following the initial newborn exam, she begins to cry and says that she has no idea how to care for a baby. She doesn't know how often to feed him or how to position him for sleep. She has received paperwork describing tests and procedures to be performed before they are discharged (i.e., circumcision, hepatitis immunization, hearing screening), but doesn't understand why they are all necessary. She also wonders why there was medicine put in his eyes and why he received a shot shortly after birth. Additionally, she is quite shocked to discover that she needs a pediatrician as she thought her obstetrician would take care of the baby.

Routine newborn care encompasses not only the evaluation and health maintenance of the infant, but also the counseling and education of parents or other caregivers.

The maternal history provides pertinent information such as the presence of certain risk factors, which could affect the newborn. A comprehensive may not be readily available, especially if the mother has had limited or no prenatal care. Reviewing the maternal chart may identify maternal risk factors that could impact the health of the newborn, as well as complications of labor and delivery that could impact fetal/newborn well being and transition.

The initial physical examination should be performed within 24 hours of birth. It may demonstrate subtle differences related to the age of the infant. An infant who is 30 minutes old has not yet completed the normal transition (from intrauterine to extrauterine life) and thus, variability may exist in vital signs and examination of the respiratory, neurological, gastrointestinal, skin, and cardiovascular systems. It is therefore ideal that a comprehensive examination be performed after the infant has completed transition. In a quiet infant, the examination should proceed from the least invasive and noxious elements of the exam (auscultation of heart and lungs) to those most likely to irritate the infant (examination of the hips and eliciting the Moro reflex).

An enormous amount of information regarding the well being of an infant can be obtained by a general visual assessment. Initial observation gives an impression of healthy (stable) versus ill and term versus preterm. Gestational age is determined by assessing various physical signs and neurological characteristics that vary according to fetal age and maturity. The new Ballard scoring system provides an objective estimate of gestational age (accuracy plus or minus 2 weeks). Gestational age assessment is pertinent as it allows the clinician to plot growth parameters, and to anticipate potential problems related to prematurity/postmaturity and also to growth abnormalities such as SGA/LGA (small and large for gestational age). After assuring that the infant is stable and thus able to tolerate a full and in depth examination, the examiner should proceed in a step-wise manner, taking into account the state and tolerance of the infant.

The specific components of the typical newborn exam are listed as follows:

General: overall behavioral state, color, respiratory status; any congenital anomalies, gender

Head: occipitofrontal circumference and shape, molding (deformation of the skull caused by labor), caput succedaneum (normal scalp edema at the apex of the head secondary to the compression sustained during labor and delivery) versus cephalohematoma (subperiosteal bleeding), sutures, fontanels, scalp trauma, defects, craniotabes (soft portions of the skull which are benign).

Eyes: presence, retinal red reflex, symmetry and completeness of iris, pupil reactivity.

Ears: shape and position, skin tags.

Nose: patency of nares.

Mouth: mucosa color, palpation of palate, presence of teeth.

Neck: range of motion, length, cysts, sinuses or masses.

Chest: symmetry, pectus deformity, clavicles, breast tissue.

Respiratory: color, respiratory rate and effort, presence, quality and equality of breath sounds, and work of breathing.

Heart: rate and rhythm, presence of murmurs; situs and precordial activity.

Pulses: strength and equality in four extremities.

Abdomen: placement of the umbilicus, 3 vessels within the umbilical cord (2 arteries, 1 vein), palpation of the liver edge (not always palpable), palpation of the spleen and kidneys (not easily palpable), any masses, bowel sounds, contour (scaphoid, flat, distended).

Male genitalia: foreskin and position of urethra, palpable descended testes, scrotum with rugae, no other masses in scrotum/groin.

Female genitalia: labia majora and minora, position of urethra, discharge.

Anus: patency and position.

Extremities: number of digits, hip exam for dysplasia/dislocation (Ortolani/Barlow), perineal creases, range of motion at all joints (especially the hips).

Spine: presence of dimples, cysts, tracts, cutaneous defects, swellings or tufts of hair.

Skin: color, rashes, ecchymoses/petechiae, perfusion, nevi, pigmentation.

Neurological system: symmetry of movement, muscle tone, posture, strength, grasp reflex, suck reflex, Moro reflex, response to being handled.

In addition to a comprehensive physical examination, several preventive measures are undertaken to ensure good newborn health. Within 1 hour of birth, infants should receive erythromycin ophthalmic ointment to both eyes to prevent ophthalmia neonatorum (from gonococcal infection). Eye prophylaxis does not prevent chlamydia conjunctivitis. Intramuscular vitamin K should also be given within 1 hour to prevent hemorrhagic disease of the newborn. Finally, bathing of skin and hair should be completed once thermal and cardiorespiratory stability have been achieved in order to reduce skin bacterial colonization.

Screening for hearing, metabolic, endocrine, and hematologic disease should also be done prior to discharge. The State of Hawaii has recently expanded the newborn screening program to test for over 30 disorders. The previous newborn screen tested for 7 disorders: hypothyroidism, phenylketonuria (PKU), congenital adrenal hyperplasia (CAH), galactosemia, sickle cell anemia, biotinidase deficiency, and maple syrup urine disease (MSUD).

Hepatitis B immunization is offered to all infants prior to discharge. If a mother is hepatitis B surface antigen (HBsAg) positive, the immunization should be administered along with hepatitis B immune globulin.

Anticipatory guidance is a major part of providing care to the healthy newborn. Educating parents about the care of their baby, especially new mothers, is of utmost importance. Nutrition is a primary educational objective. All babies must have an appropriate feeding routine established prior to discharge. Breast-feeding and breastmilk are the most beneficial for the infant as well as the mother. The mother should be counseled on the nutritional and immunological benefits of breastmilk (e.g., provides protection against illnesses such as gastroenteritis and otitis media). In cases where breastfeeding is not feasible (medically contraindicated or lack of maternal interest), then it is imperative that the infant successfully establishes bottle feeding prior to discharge. A newborn feeds every 1 to 4 hours, with longer intervals expected in formula fed infants as breastmilk tends to empty from the stomach faster than formula. A typical feeding session should last approximately 20-30 minutes.

Prior to discharge the infant should have voided and passed meconium. The first void may not occur until 16 hours of life, but in general 90% of babies will have voided by this time. In addition, 98% of infants have had their first stool by 24 hours of age. The mother should be counseled on the change in appearance of stool from meconium (dark green sticky sludge) to transitional to normal milk feeding stools and the variability between formula fed stools (tends to be brown) and breast fed stools (tends to be yellow, loose and seedy). The mother should also be aware of the appropriate number of wet diapers per day. By the end of the first week, the infant should be voiding 5 to 7 times per day.

It is essential to discuss sleep position, since prone sleeping is a known risk factor for sudden infant death syndrome. Parents should be instructed to put their infant to sleep in a supine position. Pillows, blankets and thick comforters may pose a suffocation risk and should not be present in a crib or bassinet.

General safety issues should also be addressed. The law requires rear facing car seats for infants less than 1 year of age and less than 20 pounds. Parents should be warned to never leave an infant unattended on a raised surface, in a bathtub or near water (beach, pool, bucket, etc.). Parents should also be instructed about thermal regulation. Because infants lose much of their heat from their heads, caps should be used in the hospital and in cold environments. Otherwise, newborns should be dressed as is appropriate for their immediate environment.

Caregivers should know their physician's name, office number and location, and an after hours contact number. Additionally, they should be aware that in a true emergency, 911 should be called.

Parents should anticipate that their baby may lose up to 10% of their birthweight within the first 3 to 5 days of life. The baby should regain or exceed their birthweight by 2 weeks of age.

Peeling skin is normal and does not, in general, benefit from lotions. Sponge baths should be done until the umbilical cord falls off. The drying of the cord can be aided by wiping the base with rubbing alcohol when the diaper is changed.

Circumcision is the elective surgical removal of the penile foreskin. There are no true medical indications for circumcision in the newborn. All newborns have some degree of phimosis (inability to fully retract the foreskin). It has been demonstrated that there is a decreased incidence of urinary tract infections in the first year of life in circumcised male infants. Contraindications to circumcision include hypospadias, bleeding disorders, and small penile size. Local anesthesia should be used.

Pseudomenses occurs in many female neonates. Small amounts of blood tinged mucus or frank blood may be passed vaginally within the first two weeks of life. This is due to withdrawal from the high hormone levels that the infant was exposed to in utero. Anticipatory counseling prevents unnecessary anxiety when this occurs.

Physiologic jaundice is common in the first few days of life. Risk factors for pathologic jaundice include O+ maternal blood type, bruising/cephalohematoma, prematurity, infants of diabetic mothers, polycythemia, and ethnic groups (males) at risk for G6PD deficiency.

A baby's first follow up appointment may be scheduled 2 weeks after discharge for infants who remain in the hospital for more than 48 hours after delivery. However, many physicians choose to see the baby 1 to 2 days after discharge. This is especially the case for infants discharged from the hospital at less than 48 hours of age, in accordance with American Academy of Pediatrics recommendations.

Questions

1. List three disease prevention measures routinely administered to all newborns.
2. List three early disease detection measures routinely administered to all newborns.
3. True/False: Abnormal vital signs within the first 30-60 minutes of life are always pathologic and indicate an unhealthy newborn.
4. True/False: Breast milk is associated with a decrease in the incidence of several common infections.
5. True/False: Circumcision should be routinely recommended based on medical advantages.
6. True/False: Normal stools from breast fed infants appear to be loose, yellow and seedy.

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Answers to questions

1. Vitamin K prophylaxis, antibiotic eye prophylaxis, bathing, and hepatitis B immunization. Breast feeding should also be considered to be an infection prevention/modifying measure.
2. Newborn blood and metabolic disease screening, hearing screening, physical examination.
3. False
4. True
5. False
6. True

Chapter III.2. Neonatal Hyperbilirubinemia

Carol Hirai, MD

Case 1

This is a jaundiced, 4 day old, 3.1 kg, appropriate for gestational age (AGA) Asian female infant born at term to a 25 year old A+ primiparous woman with gestational diabetes. The pregnancy was otherwise uneventful. Labor was augmented with Pitocin. The baby was discharged home on day of life 2 at which time her weight was down 4% from birth weight and she had mild facial jaundice. In the hospital, she was breast fed every 3 hours and had 2 wet diapers and one meconium stool over a 24 hour period. On day 3, her parents gave her water on two occasions as she appeared hungry despite regular and frequent breast feeding attempts. In addition, they noted an increase in the degree of jaundice, but failed to address it after being reassured by family members that jaundice is common. They also had an appointment to see their pediatrician the following day. In the office, on day 4, mother reports that she is breastfeeding the baby every three hours and that there have been 2 wet diapers per day. The urine is described as dark yellow in color and the stools appear dark green.

Exam: VS T 37.8, P 162, RR 55, BP 63/45. Weight 2.7 kg (25%ile), length 50 cm (75%ile), head circumference 34 cm (75%ile). The infant is jaundiced and irritable. The anterior fontanel is slightly sunken, the oral mucosa is tacky, and there is jaundice to the lower extremities. No cephalohematoma or bruising is present. The sclera of both eyes are icteric. Muscle tone and activity are normal. The remainder of the physical exam is normal.

The total bilirubin is 20 mg% with a direct fraction of 0.7 mg%. She is admitted to the hospital for phototherapy, supplementary formula feedings, and lactation consultation. By the following day, the bilirubin has decreased to 12 mg% and she is discharged home on breast milk feedings. The baby is scheduled for follow-up with both the pediatrician and the lactation consultant.

Case 2

A 4 day old, 36 week gestation male presents to his primary care physician with worsening jaundice. The maternal blood type is 0+. He was discharged home on day 2 of life after successfully breastfeeding for a 24 hour period. At the time of discharge, his physical exam was remarkable for mild jaundice and a cephalohematoma. At today's visit there is an 8% weight loss from birth and a history of "fair" urine output and yellow stools. He is markedly jaundiced and has a resolving cephalohematoma. Other physical exam findings are remarkable for a normal cry, flat anterior fontanelle, moist oral mucosa and a normal neurologic examination. The total bilirubin is 27 mg% with a direct fraction of 1 mg%. He is admitted to the hospital where phototherapy is initiated. His blood type is A+ with a positive direct Coombs. The hematocrit is 42% with a reticulocyte count of 12% and the pathologist identifies spherocytes on the blood smear. The G6PD is pending. After one hour of phototherapy, a repeat bilirubin is 25 mg%. The G6PD is normal. The decision is made to perform a double volume exchange transfusion. The infant remains on phototherapy for an additional 2 days and is discharged home after being off phototherapy for 1 day. The serum bilirubin on the day of discharge is 12 mg% and he passes an auditory brainstem response test.

More than 50% of term neonates become jaundiced (1). In this community (Hawaii), hyperbilirubinemia is one of the major reasons for re-hospitalization within the first two weeks of life. The primary reason for the level of concern over jaundice and hyperbilirubinemia in the newborn is the association of hyperbilirubinemia with kernicterus, which is a rare, but devastating neurologic complication of hyperbilirubinemia. Kernicterus can occur without signs and symptoms (2), but acute kernicterus in term babies is usually characterized by changes in muscle tone, drowsiness, poor feeding, a high pitched cry, apnea, possible seizures, fever, and death (3). Neurologic sequelae include dystonia and athetosis, upward gaze abnormalities, sensorineural hearing loss, intellectual deficits and tooth enamel dysplasia (3). In term patients, the MRI has increased signal intensity in the globus pallidus on T2 images (2). Although kernicterus is rare, it is potentially preventable and it is being seen with increasing frequency. This has prompted a recent Joint Commission on Accreditation of Healthcare Organizations Sentinel Event Alert (4).

The assessment and management of hyperbilirubinemia can be confusing. For instance, a bilirubin of 11 mg% has a different significance under different circumstances. It would be considered physiologic (not pathologic) in a 4 day old term breast fed baby, while the same level would be pathologic on day 1. A serum bilirubin of 11 mg% would also be concerning in a sick, two day old, 27 week gestation premature infant. Clinical decision-making is based on serum bilirubin values which are not directly reflective of risk for neurotoxicity (3). In an attempt to assist physicians with this common problem, the AAP released a practice parameter in 1994 on the Management of Hyperbilirubinemia in the Healthy Term Newborn (5). According to the commentary from the AAP Subcommittee on Neonatal Hyperbilirubinemia in 2001, this practice parameter is currently being revised (6).

Hyperbilirubinemia is more common in neonates due to the shortened life span of their red blood cells, declining hematocrit, immature liver uptake and conjugation of bilirubin, and increased intestinal reabsorption of bilirubin. Hemoglobin breakdown releases iron, carbon monoxide, and biliverdin. The latter is reduced to bilirubin, which enters the liver. Uridine diphosphate glucuronyltransferase (UDPGT) conjugates bilirubin into an excretable form. Intestinal bacteria can deconjugate bilirubin allowing for reabsorption of bilirubin into the circulation. This increased enterohepatic circulation occurs particularly in preterm neonates with diminished stool passage. In Asians, a variant in the UDPGT has been associated with hyperbilirubinemia.

Infants with red blood cell membrane G6PD (glucose-6-phosphate dehydrogenase) deficiency have a tendency for hemolysis and hyperbilirubinemia. In G6PD deficiency, hyperbilirubinemia can occur despite minimal evidence for hemolysis. Also, decreased conjugation of bilirubin has been described in G6PD deficiency.

Most unconjugated bilirubin is bound to albumin, but free unconjugated bilirubin (a form unbound to albumin) can enter the brain (i.e., it can cross the blood brain barrier). Sulfonamides are contraindicated in the neonatal period because they displace bilirubin from albumin. Conditions that disrupt the integrity of the blood brain barrier, such as infection (e.g., sepsis, meningitis, congenital viral infections), acidosis, prematurity, and hyperosmolarity, place the infant at increased risk for kernicterus. Hemolytic causes of hyperbilirubinemia (e.g., Rh incompatibility and G6PD deficiency) have higher risks of kernicterus compared to other causes of jaundice at comparable bilirubin levels.

Bilirubin may be the toxic substance responsible for kernicterus, but this is not a certainty. Very high bilirubin levels (in the 30 mg% range) most often do not result in kernicterus if no hemolytic disease is present. However, bilirubins in the 20 mg% range due to Rh incompatibility or G6PD deficiency, often result in kernicterus. The paradox that a very high bilirubin due to non-hemolytic causes has a lower kernicterus risk while a moderately high bilirubin due to Rh incompatibility or G6PD deficiency has a higher kernicterus risk, suggests that bilirubin itself may not be the direct cause of kernicterus. Bilirubin may only be a marker of the true toxic substance that causes kernicterus. This phenomenon may explain why the risk of kernicterus is not determined by bilirubin levels alone.

Jaundice can be detected clinically with tactile blanching of the skin revealing an underlying yellow color. The examination should be done in a well-lit, neutral light. Jaundice usually begins on the face and progresses caudally. The presence of scleral icterus should be assessed. Generally, the farther the jaundice progresses down the body, the higher the total serum bilirubin (3). The more intense the color (which can approach a yellow-orange) also suggests a higher total serum bilirubin. Jaundice may be clinically detected with a total serum bilirubin of 5 mg%. The presence of jaundice in particularly dark skinned newborns can be difficult to assess. Any time there is uncertainty, the recommendation is to check a total serum or transcutaneous bilirubin. Universal screening has been recently recommended, perhaps simultaneously with the newborn screen. If a patient is under phototherapy, jaundice is difficult to visually assess because phototherapy preferentially reduces bilirubin concentrations near the skin. If assessing a patient under phototherapy, jaundice severity is best determined by examining unexposed sites (e.g., under the eye shield) and phototherapy should be interrupted during the exam. If the skin is green or bronze colored, this suggests an elevated direct (conjugated) bilirubin fraction, so a fractionated bilirubin should be obtained. The patient should also be assessed for pallor, plethora and hepatosplenomegaly.

It is essential to distinguish whether the jaundice is physiologic or pathologic. Jaundice noted within the first 24 hours is pathologic and a total serum bilirubin should be drawn. Early jaundice is usually related to hemolysis, infection, drug effect, neonatal hepatitis or liver enzyme defects (e.g., Crigler-Najjar-deficiency of UDPGT) (7). A total bilirubin greater than 17 mg% in a full term neonate is pathologic (2). Jaundice that persists beyond 2 weeks should be evaluated beginning with a fractionated bilirubin (5). Direct hyperbilirubinemia is also considered pathologic, (i.e., direct bilirubin >1.5-2 mg% or > 20% of the total bilirubin) (8).

Direct (conjugated) hyperbilirubinemia cases are relatively uncommon. The differential diagnosis includes neonatal hepatitis, biliary atresia, sepsis, metabolic disorders (e.g., galactosemia), and hepatotoxicity from hyperalimentation. A detailed discussion of direct hyperbilirubinemia is beyond the scope of this chapter. One of the principal diagnoses to exclude is biliary atresia which is associated with dark urine or light colored stool. Early surgical intervention done prior to 2 months of age reduces mortality and the probability of future liver transplantation (refer to the chapter on biliary atresia).

Indirect (unconjugated) hyperbilirubinemia, is more common and presents a risk for kernicterus. The most common causes of indirect hyperbilirubinemia are physiologic, breast milk, breast feeding with a large postnatal weight loss (3), ABO incompatibility, cephalohematoma, bruising, G6PD deficiency, and East Asian ethnicity. Of these, G6PD deficiency poses a higher risk of kernicterus, but ABO incompatibility is a more common reason for exchange transfusion. Rh incompatibility is less common, but represents a high risk of kernicterus. Breastfeeding jaundice is related to inadequate intake by the newborn (i.e., components of poor feeding and dehydration are contributory). Breast milk jaundice (i.e., due to breast milk itself) has its onset later than breastfeeding jaundice. It is related to increased enterohepatic circulation and is relatively uncommon. Uncommon causes of indirect hyperbilirubinemia include other RBC membrane defects (e.g., hereditary spherocytosis) and hemoglobinopathies. In the pilot kernicterus registry, 31% of the cases were idiopathic (no identified cause), approximately equal to the incidence associated with G6PD deficiency (3).

A rise in bilirubin of greater than 0.5 mg% per hour and failure to control hyperbilirubinemia despite phototherapy are suggestive of hemolytic disease. ABO incompatibility occurs in approximately 20% to 25% of pregnancies of which significant hemolysis occurs in 10%. G6PD deficiency (X-linked recessive) occurs in African, Mediterranean, and Southeast Asian ethnic groups. In our community, some pediatricians routinely screen for G6PD in males delivered to mothers of high risk ethnic groups (e.g., Filipino).

Prenatal testing includes maternal blood typing and screening for antibodies to major RBC antigens (1). Rh incompatibility occurs with an Rh negative mother (usually not a primigravida) and an Rh positive baby. The routine use of RhoGAM at 28 weeks gestation and following delivery or pregnancy termination is generally effective in preventing maternal Rh sensitization (i.e., the production of anti-Rh antibodies by the mother). An adequate amount of RhoGAM must be given to neutralize the amount of Rh Ag or the volume of blood from a feto-maternal transfusion. Thus, the incidence of Rh isoimmunization and Rh incompatibility is uncommon. The Rh antigen is markedly more antigenic than the A or B antigen. In situations where the maternal blood type and antibody screening results are unknown, an Rh and Coombs test should be performed on the baby's blood (1).

In ABO incompatibility, the mother's blood type is O. More commonly, the babies blood type is A rather than B. Hemolysis in ABO isoimmunization usually has a positive direct antiglobulin testing (DAT), also known as a direct Coombs test. Clinically significant hemolysis is associated with a decreasing hemoglobin, hematocrit and an elevated reticulocyte count. Due to phagocytic removal of antibody and portions of the RBC membrane, the smear in ABO incompatibility may have spherocytes, mimicking spherocytosis. Therefore, a CBC with differential, reticulocyte count and a smear should be requested with suspected hemolysis. Nucleated RBCs may also be present with more severe causes of hemolysis, but is classically associated with Rh incompatibility.

If the baby is at risk for G6PD deficiency or other hemolytic diseases, appropriate testing should be done. When a G6PD level is obtained, it is important to realize that false negatives may occur in the face of active hemolysis because G6PD is increased in nucleated red blood cells.

An evaluation should be done for newborns with feeding intolerance, behavioral changes, hepatosplenomegaly, excessive weight loss, and instability of vital signs regardless of clinical detection of jaundice. Urine that is positive for reducing substances, but negative for glucose is suggestive of galactosemia. Galactosemia, a cause of direct hyperbilirubinemia, is one of the over 30 metabolic disorders included in the expanded newborn screen.

Educating parents about proper infant feeding practices (both breast and bottle), detecting their infant's hydration status, observing changes in behavior, and how to detect and report worsening jaundice, are extremely important anticipatory guidance measures. Parents should also be counseled that jaundice is common, but in rare instances, it can lead to severe morbidity and mortality which is largely preventable. At follow-up, the primary care physician should document the presence/absence of jaundice and/or the serum bilirubin level. The pediatrician's goal is to discharge a functional maternal-infant dyad with early follow up (in 1-2 days) if the infant is discharged from the hospital at less than 48 hours of age. If certain risk factors exist such as blood group incompatibility or prematurity, or if early follow-up cannot be scheduled, discharge should be delayed until after the infant has been monitored for an appropriate period of time. Some of the patients with kernicterus had a bilirubin of less than 25 mg% and did not have predictable risk factors (9). Potential separation of the parent and newborn needs to be minimized and weighed against the risks of hyperbilirubinemia complications. In this community, most mothers are discharged within 48 hours of a vaginal delivery and 3-4 days post C-section. Discharging the mother prior to the newborn can affect bonding and breastfeeding. This needs to be weighed against the risk for significant hyperbilirubinemia and compliance with follow up.

The clinician should be responsive to parents who are concerned about their child's degree of jaundice, feeding frequency or volume, drowsiness, and/or irritability (3). Caution should be used when sending patients home while awaiting lab results. Never presume that a lab value is falsely elevated. Parents should also be counseled to seek medical attention for jaundice that persists beyond 2 weeks of age.

Bhutani developed an hour specific bilirubin nomogram in healthy term and near term newborns with a negative direct Coombs (12). The patient population consisted of term and near-term appropriate for gestational age (AGA) newborns. Total serum bilirubins (TSB) of greater than or equal to 8 mg% at 24 hours, greater than or equal to 14 mg% at 48 hours, and greater than or equal to 16 mg% at 72 hours were above the 95th percentile. A TSB of greater than or equal to 17 mg% during the first week of life was above the 95th percentile. This group is at higher risk for bilirubin-induced neurologic dysfunction (BIND), including kernicterus. Bhutani advocates universal bilirubin screening with early follow up to also catch neonates who may move up from the lower percentiles.

The 1994 AAP Practice parameter (5) is an appropriate guideline for managing jaundice in the healthy term newborn without hemolysis. The guideline has age-based recommendations for therapy. At 25 to 48 hours, phototherapy is recommended at a bilirubin of greater than or equal to 15 mg%. At 49 to 72 hours, the threshold increases to 18 mg%. From greater than 72 hours, the threshold is 20 mg%. If G6PD deficiency or other kernicterus risk factors are present, it is advisable to have a lower threshold to begin phototherapy. The AAP Practice parameter also contains recommendations for exchange transfusion. Table 1 below describes hyperbilirubinemia treatment guidelines for preterm infants. Table 2 below describes hyperbilirubinemia treatment guidelines for term infants.

Table 1 - Suggested Maximum Indirect Serum Bilirubin Concentrations (mg%) in Preterm Infants (10)

Birthweight (g)	Uncomplicated	Complicated*
<1,000	12-13	10-12
1,000-1,250	12-14	10-12
1,251-1,499	14-16	12-14
1,500-1,999	16-20	15-17
2,000-2,500	20-22	18-20

For table 1 above, phototherapy is usually started at 50% to 70% of the maximum indirect levels. If values greatly exceed this level, if phototherapy is unsuccessful in reducing the maximum bilirubin level, or if there are signs of kernicterus, exchange transfusion is indicated. *Complicated cases include those associated with perinatal asphyxia, acidosis, hypoxia, hypothermia, hypoalbuminemia, meningitis, intraventricular hemorrhage, hemolysis, hypoglycemia, or signs of kernicterus (10).

Table 2 - Treatment Strategies for Indirect Hyperbilirubinemia in Healthy Term Infants Without Hemolysis (10)

Age (hrs)	Phototherapy	Intensive phototherapy and preparation for exchange transfusion if phototherapy fails	Exchange transfusion
24-48	15-18	25	20
49-72	18-20	30	25
>72	20	30	25

If the initial bilirubin on presentation is high, intense phototherapy should be initiated and preparation made for exchange transfusion. If the phototherapy fails to reduce the bilirubin level to the levels noted on the column to the right (table 2), an exchange transfusion should be initiated. Intensive phototherapy usually reduces serum bilirubin levels 1 to 2 mg% in 4 to 6 hours. This is often done with IV fluid administration at 1 to 1.5 times maintenance and oral alimentation should continue (10).

Hyperbilirubinemia of the degree noted in the 24-48 hours line of table 2, is unusual and should suggest hemolysis, concealed hemorrhage, or causes of conjugated (direct) hyperbilirubinemia (10).

Jaundice suddenly appearing in the second week of life or continuing beyond the second week of life with significant hyperbilirubinemia levels to warrant therapy should be investigated in detail, as it most probably is due to a serious underlying cause such as biliary atresia, galactosemia, hypothyroidism, or neonatal hepatitis (10).

Supplementing feeds with water or dextrose has been associated with higher bilirubin levels. Use of metalloporphyrins which inhibit bilirubin production has been limited to study trials in newborns. The mainstay of treatment is phototherapy with a wavelength of 450 nm. It induces photoisomerization of bilirubin, forming lumirubin which is water soluble and excreted in the urine. Phototherapy is generally delivered by fluorescent lights, spot lights, or fiberoptics, the latter generating less heat. Unless there is a high risk for an exchange transfusion, phototherapy can usually be discontinued for an hour to allow for neonatal care. Discontinuation of phototherapy in a term baby without hemolysis generally is not associated with rebound hyperbilirubinemia, i.e., a significant increase in bilirubin.

Although phototherapy may be commonly thought of to prevent kernicterus, this is less than accurate, since if the patient is at significant risk of kernicterus, an exchange transfusion should be done. Phototherapy's major role is to avoid an exchange transfusion. By implementing phototherapy, the belief is that this will reduce the likelihood that bilirubin levels will reach these exchange transfusion levels, thus avoiding an exchange transfusion.

In term neonates with hemolytic disease, if the bilirubin approaches 20 mg% despite medical management, informed consent should be obtained for an exchange transfusion. In preterm neonates less than 37 weeks gestation, most neonatologists will await serum bilirubin levels of 15-20 mg% before considering an exchange (11). Exchange transfusion removes bilirubin and antibodies causing hemolysis. Twice the patient's blood volume is exchanged (i.e., double volume exchange) while monitoring cardiovascular stability. Risk factors include those related to catheters, electrolyte imbalance and blood products superimposed onto preexisting medical problems. Thrombocytopenia is common. Necrotizing enterocolitis, graft versus host disease, and death have also been reported as complications of exchange transfusion.

Does phototherapy reduce the need for an exchange transfusion? In ABO incompatibility, prophylactic phototherapy was not shown to be superior to no therapy at all in this regard (13). However, phototherapy intensities have increased since the time of that study and anecdotally, it appears that fewer exchange transfusions are being done, possibly due to more routine use of phototherapy. Additionally, phototherapy appears to be harmless, so its utilization is reasonable to treat moderately high bilirubin levels.

Although extreme bilirubin levels are associated with kernicterus, the adverse effects of moderate hyperbilirubinemia may be more difficult to identify. For example, subclinical adverse effects, learning disabilities or behavioral disorders would be more difficult to causally link to moderate hyperbilirubinemia, since this would only be manifested in later childhood.

Most cases of hyperbilirubinemia resolve without sequelae. However, there may be impairment of auditory nerve conduction (2). After significant hyperbilirubinemia, the patient should undergo auditory brainstem response testing (6).

Questions

1. Which of the following factors leads to neonatal hyperbilirubinemia?
    a. Shortened neonatal red cell life span.
    b. Impaired excretion of unconjugated bilirubin.
    c. Limited conjugation of bilirubin in the liver.
    d. Increased enterohepatic circulation.
    e. All of the above.

2. True/False: Hemoglobin degradation results in the formation of biliverdin and carbon monoxide.

3. A total serum bilirubin >17 mg% in a term neonate is:
    a. physiologic
    b. pathologic

4. In G6PD deficiency, there is hyperbilirubinemia on the basis of:
    a. hemolysis
    b. decreased conjugation
    c. both
    d. neither

5. True/False: In Asians, a variant in UDPGT is associated with neonatal hyperbilirubinemia.

6. True/False: Systemic sulfonamide medications are avoided in the newborn because they displace bilirubin from albumin and increase free bilirubin.

7. True/False: Breast milk jaundice is more common than breast feeding jaundice.

8. True/False: Supplementation of breast feeding with water or dextrose lowers the serum bilirubin.

9. True/False: Discontinuation of phototherapy in a healthy, term neonate is usually associated with rebound hyperbilirubinemia.

10. Which of the following factors should be strongly considered in determining whether an exchange transfusion is indicated in a term neonate with an indirect bilirubin of 21 mg%.
    a. Age of the neonate (time since birth).
    b. Whether the cause is hemolytic or non-hemolytic.
    c. The presence of other clinical factors such as intraventricular hemorrhage or meningitis.
    d. All of the above.
    e. None of the above.

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Answers to questions
1.e, 2.True, 3.b, 4.c, 5.True, 6.True, 7.False, 8.False, 9.False, 10.d

Chapter III.3. Newborn Resuscitation
Sheree Kuo, MD

You are asked to attend an emergent cesarean section delivery of a 40 weeks' gestation infant with non-reassuring heart tones. Mother is a 30 year old gravida 1 married woman who was admitted in active labor four hours ago. She had good prenatal care starting at 6 weeks gestation and her pregnancy has been uncomplicated. Prenatal labs are as follows: blood type A+, antibody negative, rubella immune, VDRL non-reactive, Gonococcus negative, Chlamydia negative, HIV negative, Hepatitis B surface antigen negative, and Group B Strep negative. Prior to delivery, mother received general anesthesia, fentanyl and IV fluids, but no other medications. Membranes are ruptured at the time of delivery revealing bloody amniotic fluid, but no meconium. The obstetrician suspects placental abruption.

At delivery, you receive a floppy, apneic, and blue term male infant. You bring him to the warming table where he is quickly positioned, dried, stimulated and given free-flow oxygen. At 30 seconds of life, he remains apneic and cyanotic. His heart rate is 30 beats per minute. You administer positive pressure ventilation with 100% FiO2 and note good chest wall rise with each positive pressure breath. The infant continues to be apneic and bradycardic with a heart rate of 40 bpm. Chest compressions are begun and positive pressure ventilation is continued. Following 30 seconds of coordinated ventilation and chest compressions, his heart rate is still 40 bpm. You intubate the infant while the nurse draws up 0.1 cc/kg of 1:10,000 concentration of epinephrine to be given via the endotracheal tube. There is no improvement in his heart rate following administration of epinephrine. You then catheterize the umbilical vein and give the second dose of epinephrine intravenously. The infant remains bradycardic. Positive pressure ventilation and chest compressions are continued as you reassess the infant. Good breath sounds are heard bilaterally, but his skin remains pale and mottled and pulses are difficult to palpate. Suspecting hypovolemia, you then administer 10cc/kg of normal saline through the umbilical vein catheter over 5 minutes. The infant's heart rate rises to 150 and his color gradually improves. You check the security of the endotracheal tube and umbilical catheter and prepare for transport to the newborn intensive care unit.

The transition from intrauterine to extrauterine life occurs without incident in approximately 90% of all births. However, 10% of newborns will require some assistance with breathing at birth, while 1% will need extensive resuscitative measures in order to survive. Worldwide, the outcome of more than 1 million newborns per year may be improved with the use of neonatal resuscitative measures.

In utero, the lungs do not perform gas exchange and accordingly, pulmonary blood vessels are markedly constricted. Oxygenated blood flows from the placenta through the umbilical vein to the right heart where the majority of the blood is shunted to the aorta through the foramen ovale and patent ductus arteriosus. Seconds after birth, three major changes occur in the newborn in order to transition to extrauterine life. First, fluid in the alveoli is absorbed into lung tissue and is replaced by air. Next, the umbilical cord is clamped, disconnecting the infant from the low resistance placental circulation and increasing systemic blood pressure. Lastly, the pulmonary vasculature relaxes in response to increased oxygen levels in the lungs causing a dramatic increase in pulmonary blood flow. The right to left shunt through the patent ductus arteriosus decreases, becoming bi-directional and the foramen ovale functionally closes in association with the increase in blood return to the left atrium. Infants who fail to complete the transition to extrauterine life may exhibit cyanosis, bradycardia, hypotension, depressed respiratory drive and/or poor muscle tone (1).

Although it is impossible to consistently predict the need for active newborn resuscitation, many antepartum and intrapartum maternal and obstetrical conditions are associated with increased risk to the newborn. Antepartum risk factors include: maternal diabetes, hypertension (pregnancy induced or chronic), chronic maternal illness, anemia or isoimmunization, previous fetal or neonatal death, bleeding in the second or third trimester, maternal infection, polyhydramnios, oligohydramnios, premature rupture of membranes, post-term gestation, multiple gestation, size-dates discrepancy, maternal drug therapy, maternal substance abuse, fetal malformation, diminished fetal activity, no prenatal care and maternal age <16 or >35 years. Intrapartum risk factors include: emergency cesarean section, forceps or vacuum-assisted delivery, breech or other abnormal presentation, premature labor, precipitous labor, chorioamnionitis, prolonged rupture of membranes, prolonged labor, prolonged second stage of labor, fetal bradycardia, non-reassuring fetal heart rate patterns, use of

general anesthesia, uterine tetany, narcotics administered to mother within 4 hours of delivery, meconium-stained amniotic fluid, prolapsed cord, abruptio placentae, and placenta previa.

A team approach should be applied to all potential newborn resuscitations. Appropriate preparation for an anticipated high-risk delivery requires detailed communication between the mother's caregivers and the newborn resuscitation team. At least one person capable of initiating resuscitation should attend every delivery and be responsible for the care of the infant. Resuscitations involving assisted ventilation and chest compressions require at least two experienced persons. Three or more trained persons would ideally be available for an extensive resuscitation requiring medication administration.

The need for resuscitation should be determined immediately after birth. Most term newborn infants who transition normally to the extrauterine environment (with crying, pink color and good tone) can remain with the mother to receive routine care. Indications for further assessment under a radiant warmer include meconium in the amniotic fluid or on the skin, absent or weak responses, persistent cyanosis and preterm birth. Following this initial assessment, all subsequent assessments are based on the triad of breathing, heart rate and color. Regular respirations are adequate if they can maintain a heart rate of >100 bpm and good (pink) color. Gasping, apnea and central cyanosis generally indicate the need for additional interventions. A newborn's heart rate can be assessed by either auscultating the precordium or counting pulsations through palpation of the base of the umbilical cord. Heart rate should be >100 bpm in the uncompromised newborn. A newborn's color is best determined by examining the face, trunk, and mucous membranes. An uncompromised infant will maintain pink mucous membranes without supplemental oxygen. Cyanosis of the distal extremities or acrocyanosis, is a normal finding at birth and should not be used to determine the need for supplemental oxygen.

For the infant who is not vigorous at delivery, the basic steps in newborn resuscitation include providing warmth, positioning and clearing the airway, drying and stimulating the infant and providing supplemental oxygen as needed. Warming the infant immediately after birth will decrease cold stress and oxygen consumption. This can be done by simply placing the infant under a radiant warmer, quickly drying the skin, removing wet linens and wrapping the infant in pre-warmed blankets. The airway is cleared first by positioning the infant supine or lying on its side with the head in a slightly extended position. If airway secretions are concerning, the infant can be suctioned, mouth first, then nose, with a bulb syringe or suction catheter. Additional stimulation may be provided by gently rubbing the back or flicking the soles of the feet if an infant fails to initiate effective respirations following drying and suctioning. 100% free-flow oxygen should be administered by mask or oxygen tubing to the breathing newly born infant with cyanosis, bradycardia or other signs of distress. These initial steps should be performed during the first 30 seconds of life and the infant should then be reevaluated for breathing, heart rate and color (1,2).

If the infant continues to be apneic, is gasping, has a heart rate of less than 100 bpm and/or has persistent central cyanosis despite 100% free flow oxygen, then positive pressure ventilation with a bag and mask should be administered. Adequate ventilation is the most important and most effective step in cardiopulmonary resuscitation of the compromised newborn infant. Before assisting ventilation with a bag and mask, the proper size mask must be selected, the airway must be clear, and the baby's head should be positioned. The mask should cover both nose and mouth to achieve a tight seal with the face. Noticeable chest wall rise, bilateral breath sounds and improved color and heart rate are indications that ventilation is adequate. Breaths should be delivered at a rate of 40 to 60 per minute. After 30 seconds of proper ventilation, breathing, heart rate and color should be reevaluated. If the baby is breathing spontaneously and the heart rate is greater than 100 bpm, positive pressure ventilation can be stopped. However, if the infant's heart rate is greater than 60, but less than 100 bpm, then positive pressure ventilation must be continued.

If the infant's heart rate remains less than 60 bpm following the initial 30 seconds of positive pressure ventilation, it is likely that blood oxygen levels are low and myocardial contractility (and cardiac output) is poor. Chest compressions must be started and assisted ventilation continued until the myocardium recovers adequate function. Two people are required to administer chest compressions: one to administer compressions and one to continue ventilation. To perform chest compressions, enough pressure is applied to the lower third of the sternum to depress the sternum to a depth of approximately one third of the anterior-posterior diameter of the chest then released to allow the heart to refill. Poor technique may result in liver laceration and/or rib fracture. Three compressions should be administered for every one assisted ventilation so that 90 compressions plus 30 breaths are given each minute. Reevaluation of respiration, heart rate and color should be done after 30 seconds of coordinated ventilation and chest compressions. If the heart rate is above 60 bpm, then chest compressions can be stopped, but assisted ventilation should continue until the heart rate is greater than 100 bpm and there is spontaneous breathing. However, if the infant is not improving, that is, the heart rate remains below 60 bpm despite 30 seconds of well coordinated ventilation and chest compressions, then epinephrine should be given.

Epinephrine is a cardiac stimulant that increases contractility (inotropy) and heart rate (chronotropy) while causing peripheral vasoconstriction (alpha adrenergic effect). The recommended dose is 0.1 to 0.3 ml/kg of a 1:10,000 solution (equal to 0.01 to 0.03 mg/kg). It can be administered through an endotracheal tube for absorption by the lungs into the pulmonary veins, which drain directly into the heart. Alternatively, epinephrine can be given into a catheter placed in the umbilical vein. This route will likely deliver more effective blood levels of the drug, but additional time is required to insert the catheter. Thirty seconds following administration, an increase in heart rate to more than 60 bpm should be observed. If the heart rate remains depressed (<60 bpm) repeat doses of epinephrine may be given every 3 to 5 minutes. In the meantime, good chest movement, equal bilateral breath sounds, and well coordinated chest compressions to an appropriate depth must all be ensured. If the infant displays pallor, poor perfusion and/or there is evidence of blood loss, hypovolemic shock should be considered in the infant who has not responded to resuscitative efforts.

The recommended solution for acutely treating hypovolemia in the newly born infant is normal saline. Alternative acceptable solutions include Ringer's lactate and O-negative blood. Volume expanders must be given intravenously, usually through an umbilical vein catheter, although the intraosseous route can also be used. The initial dose is 10ml/kg given over 5 to 10 minutes. Repeat doses may be needed if large volume blood loss has occurred. If the heart rate is detectable but remains below 60 bpm after administering adequate ventilation, chest compressions, epinephrine, and volume expanders, the possibility of metabolic acidosis should be considered. Moreover, mechanical causes of poor response including airway malformation, pneumothorax, and diaphragmatic hernia or congenital heart disease should also be considered.

If the heart rate remains absent after 15 minutes of resuscitative efforts (establishing an airway, delivering positive pressure ventilation, administering chest compressions, administering epinephrine, addressing the possibilities of hypovolemia, acidosis, congenital airway malformation or congenital heart disease) discontinuation of resuscitation may be appropriate (2).

Apgar scores are commonly recorded as part of the delivery record. Apgar scores of 8 and 9 at 1 and 5 minutes, respectively, are normal. Scores are given as noted in the table below. A one minute Apgar score of 8 is usually due to a zero score for color since truncal cyanosis is still present at one minute. A 5 minute Apgar score of 9 is normal because acrocyanosis of the feet persists for some time past five minutes. Low Apgar scores at five and ten minutes may reflect birth depression and/or need for resuscitation.

Apgar Scoring

Score	0	1	2
Heart rate	Absent	<100	>100
Respiratory effort	Absent	Slow, irregular	Good, crying
Muscle tone	Limp	Some flexion	Active motion
Reflex irritability	No response	Grimace	Cough or sneeze
Color	Blue	Extremities blue	Completely pink

Questions

1. What antepartum and intrapartum risk factors are seen in the case presented?
2. Name three major physiologic changes that must occur in the newborn shortly after birth in order to transition to extrauterine life.
3. What three elements of the newborn physical examination are reassessed every 30 seconds during resuscitation until the infant is stable?
4. Ideally, how many caregivers should be available for the resuscitation presented in the case vignette?
5. What is the most important step in cardiopulmonary resuscitation of the compromised newborn infant?
6. What are the indications for beginning assisted ventilation with a bag and mask? At what rate?
7. How can you assess whether or not assisted ventilation is adequate?
8. When should chest compressions be administered? At what rate?
9. What injuries are associated with chest compressions?
10. What is the recommended dose of epinephrine for neonates? By which routes can it be given?

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Answers to questions

1. Antepartum risk factors: None. Intrapartum risk factors: emergency cesarean section, non-reassuring fetal heart tones, use of general anesthesia, narcotics administered to mother within 4 hours of delivery, and abruptio placentae.
2. Fluid in alveoli is absorbed and air fills the air sacs, umbilical cord is clamped disconnecting the infant from the placental circulation and pulmonary vasculature must relax allowing increased pulmonary blood flow and decreased right-to-left shunting.
3. Breathing, heart rate and color.
4. Three or more trained persons would ideally be available for an extensive resuscitation requiring medication administration.
5. Ventilation of the lungs is the most important and most effective step in cardiopulmonary resuscitation of the compromised newborn infant.
6. If the infant continues to be apneic, is gasping, has a heart rate of less than 100 bpm and/or has persistent central cyanosis despite 100% free flow oxygen, then positive pressure ventilation with a bag and mask should be administered. Breaths should be delivered at a rate of 40 to 60 per minute.
7. Noticeable chest wall rise, bilateral breath sounds and improved color and heart rate are indications that ventilation is adequate.
8. If the infant's heart rate remains less than 60 bpm following the initial 30 seconds of positive pressure ventilation, chest compressions must be started and assisted ventilation continued. Three compressions should be administered for every one assisted ventilation so that 90 compressions plus 30 breaths are given each minute.
9. Liver laceration and rib fracture.
10. The recommended dose is 0.1 to 0.3 ml/kg of a 1:10,000 solution (equal to 0.01 to 0.03 mg/kg). It can be administered through an endotracheal tube or through an umbilical vein catheter.

Chapter III.4. High Risk Pregnancy
Mary Elaine Patrinos, MD

A 26 year old G1P0, O+, VDRL NR, rubella immune, HBsAg negative female at 27 weeks gestation presents to labor and delivery with a 2 day history of headache and facial swelling. Maternal history is remarkable for a single prenatal visit in the first trimester.

Exam: VS T 37, P 75, RR 14, BP 170/100. Her exam is remarkable for facial and pretibial edema and hyperreflexia.

Labs: Urine dipstick positive for 3+ protein. Ultrasound demonstrates decreased amniotic fluid. The fetus is in the breech position and no fetal abnormalities are noted. Estimated fetal weight is 650 grams.

A decision is made to deliver the infant by cesarean section following maternal treatment with betamethasone.

The risk factors identified in the above scenario include poor prenatal care, severe preeclampsia, prematurity, oligohydramnios, and intrauterine growth restriction. For the pediatrician, detailed knowledge of the maternal and pregnancy history is critical to providing timely and comprehensive care to the infant. Therapeutic interventions are planned based on the neonate's anticipated problems. Appropriate steps in preparing for the delivery of the above infant include: 1) mobilization of the high risk delivery team comprised of a physician (typically a neonatologist), neonatal nurse, and respiratory therapist, 2) notification of neonatal intensive care nursery staff, 3) preparation of exogenous surfactant for treatment of anticipated surfactant deficiency or respiratory distress syndrome (RDS), 4) planning for immediate vascular access to meet the infant's fluid and metabolic needs.

A high risk pregnancy can be defined as any pregnancy where maternal and/or fetal conditions may lead to an adverse perinatal outcome. Preterm labor (PTL) and delivery, premature rupture of membranes, multiple gestation, preeclampsia, diabetes, maternal substance abuse, and vaginal bleeding, are common high risk conditions. A pregnancy may be identified as high risk during the antepartum or intrapartum period. Indeed, lack of, limited, or late prenatal care, in and of itself, is a common high risk condition seen in urban perinatal centers. Screening tests for certain high risk problems such as diabetes, genetic conditions, and congenital anomalies are either routinely or selectively performed during the antepartum period for early recognition and intervention. This chapter will focus on a few of the more common pregnancy complications with an emphasis on neonatal outcome.

Preterm labor is defined as the onset of labor prior to 37 weeks gestation. The World Health Organization defines preterm delivery as a delivery that occurs between 20 and 37 weeks gestational age. Preterm labor is responsible for 40-50% of all preterm births. The remainder of preterm births occur from preterm premature rupture of membranes (PPROM) and maternal medical or obstetrical (maternal and/or fetal) complications (1). Most of the major risk factors for preterm delivery are: African-American ethnicity, socioeconomic status, smoking, substance abuse, poor nutrition, absent or inadequate prenatal care, history of preterm labor/delivery, uterine/cervical anomalies, uterine abnormalities (myomata, DES exposure), hypertension/preeclampsia, diabetes, multiple gestation, oligo- or polyhydramnios, vaginal bleeding, and infection.

After reviewing the list above, it is readily apparent that preterm delivery is the common denominator for many high risk conditions of pregnancy. Timely detection of preterm labor and delivery allows for prompt referral of the mother to a facility where more intensive surveillance, monitoring, and care for both mother and newborn can be accomplished (2).

The pathogenesis of spontaneous, isolated PTL is multifactorial; however, many cases appear to result from occult upper genital tract infections with activation of the decidua. Inflammatory cytokines such as interleukin-1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor-a (TNFa) have been detected in amniotic fluid in association with intrauterine infection and preterm labor. These cytokines stimulate the production of PGE2 and PGF2a which increase dramatically during labor. Although eliminating or markedly reducing the incidence of PTL seems an impossible goal when considering its multiple causes, ongoing efforts to actively treat PTL remain critical, especially for the patient population less than 32 weeks gestation. Studies assessing prevention methods such as education and surveillance programs and home uterine activity monitoring have demonstrated no benefit in reducing the frequency of preterm birth. Other strategies involved in the treatment of preterm labor are: cervical cerclage, tocolytics (beta sympathomimetics such as terbutaline and ritodrine, magnesium sulfate, prostaglandin synthetase inhibitors such as indomethacin), and antibiotics. Of these, the most frequently used methods at Kapiolani Medical Center for Women and Children are cerclage, terbutaline, magnesium sulfate, and antibiotics. Although it has been difficult to demonstrate the efficacy of tocolytics and antibiotics in clinical trials for preterm labor, these agents may provide a 48 hour latency period during which antenatal corticosteroids can be administered. Maternal and fetal side effects must be considered with the use of any intervention for PTL. Cerclage is generally limited to patients with a history of incompetent cervix. It involves placing a suture circumferentially around the internal cervical os between 12-14 weeks gestation. Maternal risks associated with cerclage placement include the risk of anesthesia, bleeding, infection, rupture of membranes, maternal soft tissue injury, and spontaneous suture displacement. The major risks to the fetus are infection and preterm birth. Terbutaline, the most commonly used beta sympathomimetic, stimulates the beta-2 receptors found in the uterus. Potential fetal side effects of beta-2 agonists include elevation in baseline heart rate, rhythm disturbances, septal hypertrophy, and hypoglycemia. Magnesium sulfate affects uterine activity by decreasing the release of acetylcholine and altering the amount of calcium pumped out of myometrial cells. Respiratory and motor depression can occur in the neonate with high maternal magnesium levels. In general, side effects to the fetus and neonate are minimal when compared to beta sympathomimetics. Given the role of prostaglandins in labor, indomethacin would seem a logical choice for a tocolytic agent. Reported fetal side effects include oligohydramnios secondary to decreased fetal urine output, ductal constriction with the potential for subsequent persistent pulmonary hypertension in the neonate, and necrotizing enterocolitis. The use of indomethacin is restricted to pregnancies at <30-32 weeks gestation and for a treatment period of less than 48 hours. The benefits of antibiotic therapy are best appreciated in relation to PPROM. Ampicillin and erythromycin have been shown to increase the latency period from the time of rupture of membranes to delivery with significant neonatal benefits (1).

The incidence of neonatal mortality and morbidity increases with decreasing gestational age. Although it is outside the scope of this chapter to address the multiple medical, psychosocial, neurodevelopmental and financial problems associated with prematurity, it should be emphasized that the "borderline viable" population of infants (<25 weeks gestational age) remain the greatest challenge. Due to their statistically poor outcomes, the question of whether or not to provide life supportive measures in the delivery room is, ideally, discussed with the prospective parents prior to delivery. The management of these most fragile newborns remains an ongoing area of controversy and debate in neonatal medicine.

Preeclampsia is defined as new onset gestational hypertension with proteinuria, with or without edema. It complicates approximately 8% of pregnancies and is a major cause of maternal and perinatal morbidity and mortality. Uteroplacental ischemia mediated by the renin-angiotensin system is one of the most fundamental abnormalities of this disorder, however, the etiology of

preeclampsia is still unknown. Predisposing factors include primiparity, younger and older age extremes, familial/genetic factors, twin gestation, diabetes, and non-immune hydrops fetalis. The oldest and most effective treatment is delivery. Additional and alternative treatment strategies such as antihypertensives and magnesium sulfate for prevention of seizures are commonly employed especially when the degree of fetal immaturity (balanced with maternal status) precludes immediate delivery. The increase in perinatal morbidity and mortality associated with preeclampsia is largely due to prematurity. Uteroplacental insufficiency and abruptio placenta contribute to poor outcomes (3). Fetal intrauterine growth restriction is a frequent and expected by product of uteroplacental ischemia. Interestingly, despite the increase in fetal growth restriction and prematurity, preeclampsia is associated with a decreased risk of cerebral palsy (4).

Diabetes mellitus is classified as type 1 (lack of insulin production or pre-gestational), type 2 (adult onset, insulin resistance). An elaborate and more detailed classification system for diabetes in pregnancy was developed by Priscilla White and later modified where type A1 is described as gestational diabetes treated with diet, and type A2 requires insulin therapy. Gestational diabetes is defined as carbohydrate intolerance first recognized during pregnancy. It accounts for the majority (80-90%) of the 3-5% of pregnancies complicated by diabetes and is caused by a 60% decrease in peripheral insulin sensitivity (a normal phenomenon in pregnancy), for which some women cannot compensate (i.e., there is a concomitant inability of the pancreas to produce adequate insulin in response to a glucose load). Because this condition is often asymptomatic, screening is indicated between 24 and 28 weeks gestation. Glucose management is strict with the recommendation to maintain levels between 60 and 120 mg/dl. It is well established that tight metabolic control is associated with a marked reduction in the fetal and neonatal complications associated with diabetes in pregnancy listed in the table below:

Fetal and Neonatal Complications of Diabetes in Pregnancy:

A. Congenital Anomalies (Type 1 DM only)
    - Caudal dysplasia (sacral agenesis)
    - Neural tube defects
    - Cardiac anomalies (transposition, VSD, hypertrophic cardiomyopathy)
B. Macrosomia (DM Types 1 and 2)
    - Hypoglycemia
    - Birth trauma
    - Perinatal asphyxia
C. Polyhydramnios (DM Types 1 and 2)
D. Hypoxia (DM Types 1 and 2)
    - Polycythemia
E. Delayed lung maturation (DM Types 1 and 2)

Congenital anomalies in infants of mothers with type 1 diabetes occurs in up to 25% of pregnancies (compared to 2-5% for non-diabetic pregnancies) depending upon the status of glucose control during embryogenesis (the first 8 weeks of pregnancy) (5). Macrosomia occurs in 25%-45% of pregnancies complicated by diabetes which is a direct result of fetal hyperglycemia and hyperinsulinemia. Neonatal management of all infants of diabetic mothers includes a thorough evaluation for birth trauma and congenital defects, screening for and management of hypoglycemia, and close scrutiny of the infant for signs of respiratory distress.

Maternal substance abuse occurs in 5-6% of all pregnancies. This condition presents the greatest clinical challenge to the pediatrician because prevention and treatment strategies are either nonexistent or unsatisfactory. Coexisting problems include sexually transmitted diseases (syphilis, HIV), tuberculosis, hepatitis, preterm labor, and both acute and long term consequences to the newborn. Agent specific neonatal outcomes are frequently confounded by polysubstance abuse, poor nutrition, poor health care and unsatisfactory home environments. In Hawaii, the most commonly abused drugs are alcohol, marijuana, amphetamines, and methamphetamines. Additional substances of abuse include cocaine, heroin, and miscellaneous other agents. As a general rule, the severity and frequency of fetal/neonatal side effects associated with maternal substance abuse is related to timing, dose, and duration of use. Heroin has been one of the best studied and well characterized due to its prolonged existence as an illicit drug. Complications of heroin addiction in pregnancy include an increased incidence of stillbirth, preterm birth, and the delivery of infants who are small for gestational age. Neonatal abstinence syndrome (symptoms of withdrawal) occur in 50%-75% of infants and usually begin within 48 hours after birth and consists of a combination of irritability, jitteriness, coarse tremors, high pitched cry, sneezing, yawning, tachypnea, poor feeding, vomiting, diarrhea, sweating, temperature instability, hyperreflexia, and, occasionally, seizures. A scoring system has been devised using the above symptoms to assist with the management of these infants. Pharmacotherapy for severe withdrawal symptoms include tincture of opium, phenobarbital, and methadone. The use of naloxone is strictly contraindicated as it can lead to acute, severe withdrawal and seizures. Methadone withdrawal seen in infants of mothers under treatment for heroin addiction has many similar characteristics to heroin abstinence syndrome. Methadone is associated with both delayed onset and increased severity of withdrawal symptoms, including seizures.

Fetal alcohol syndrome (FAS) has also been extensively addressed in the literature. Alcohol is a physical and behavioral teratogen (6). Exposure during pregnancy may result in a spectrum of symptoms secondary to varying degrees of insult to the central nervous system. Microcephaly, mild to moderate mental retardation, subtle cognitive and behavioral deficits have all been well described. Additional features of FAS include growth deficiency, short palpebral fissures, hypoplastic philtrum, thin upper lip, micrognathia, cardiac defects and a variety of other anomalies. Acute neonatal withdrawal from alcohol is rare.

No consistent or specific complications have been associated with the use of marijuana in pregnancy. Adverse pregnancy outcomes associated with cocaine abuse include higher incidence of stillbirth, asphyxia, prematurity, and babies with low birth weight and smaller heads. Symptoms of withdrawal are subtle and not well characterized. Breastfeeding is contraindicated as cocaine intoxication has been demonstrated in breast fed infants. Abuse of either amphetamine or methamphetamine during pregnancy is associated with a higher incidence of perinatal mortality, prematurity, and growth deficits. Abnormal central nervous system findings including cystic encephalomalacia and hemorrhage have also been described (6). Selective drug screening of mothers and newborns takes place routinely at most perinatal centers. Decisions regarding who to screen is often related to other perinatal risk factors such as inadequate prenatal care, previous history of substance abuse, high risk clinical signs in the mother (inappropriate or unusual behavior), history of prostitution, history of preterm labor, and presence of sexually transmitted disease(s). Documentation of fetal drug exposure by newborn urine or meconium toxicology screening typically results in referral to child protective services. All too often, these infants are placed in foster care pending rehabilitation of the mother or correction of the potentially harmful home situation.

In summary, there are many high risk conditions of pregnancy that can result in adverse neonatal outcomes, especially prematurity. It is important for the pediatrician to be fully aware of maternal risk factors so that he/she may be fully prepared to receive the newborn in the delivery room and provide ongoing care. Timely recognition of certain high-risk conditions during pregnancy often results in the transfer of the mother and fetus to a facility equipped to provide subspecialty care.

Questions

1. True/False: Preterm labor is defined as the onset of labor prior to 34 weeks gestation.

2. An effective and safe measure for treating preterm labor and delaying preterm delivery is:
    a. Antibiotics
    b. Cerclage
    c. Detection of uterine contractions through the use of home uterine activity monitoring
    d. Magnesium sulfate therapy

3. The most widely accepted explanation for the onset of preterm labor is
    a. Adrenal cortical suppression
    b. Decidual activation and inflammatory cytokines
    c. Increased levels of serum oxytocin
    d. Premature, idiopathic activation of the normal labor process

4. True/False: Preeclampsia is a complication of pregnancy associated with hypertension and proteinuria.

5. Which of the following is not a predisposing factor for preeclampsia
    a. Age
    b. Cigarette smoking
    c. Diabetes
    d. Twins

6. True/False: Naloxone is the treatment of choice for drug withdrawal in methadone addicted newborns.

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Answers to questions

1.false, 2.d, 3.b, 4.true, 5.b, 6.false

Chapter III.5. Common Problems of the Premature Infant
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This is a 1300 gram male born via normal spontaneous vaginal delivery at 30 weeks gestation to a 25 year old. G3P2 mother with a history of incompetent cervix. The mother was hospitalized at 27 weeks gestation due to cervical changes and received 2 doses of betamethasone two weeks prior to delivery. At delivery, the infant was noted to have a lusty cry. Apgar scores were 6 and 6 at one and five minutes, respectively due to poor respiratory effort, decreased tone and decreased response to stimulation. He is transported to the neonatal intensive care unit on blow-by oxygen and on admission, he is placed on nasal continuous positive airway pressure (CPAP) of 10 with an FiO2 of 0.3 (30%).

Exam: VS T36, HR 140, RR 50, BP 45/30 (mean of 38), oxygen saturation 96%. Weight 1300 gm (50th percentile), length 40 cm (50th percentile), HC 28 cm (50th percentile). His head is normocephalic with minimal molding and overlapping sutures. There are no craniofacial or oropharyngeal anomalies noted. There is fair aeration over both lung fields with clear breath sounds. He has a normal precordium and a grade 2/6 holosystolic murmur at the upper left sternal border. His pulses are equal, 2+ in strength with no radiofemoral delay. His capillary refill is 2 seconds. He has decreased tone but he responds well to stimulation and he has normal age appropriate reflexes

A chest x-ray demonstrates a normal heart size, lungs expanded to 9 ribs, and clear lung fields. On DOL (day of life) 2, the infant is taken off CPAP and placed in room air. A percutaneous central venous line is placed to provide parenteral nutrition. He is also started on small feedings of mothers' breast milk/colostrums. Thermal support is provided by an isolette. The following day he is noted to have several episodes of apnea and bradycardia. These resolve with nasal CPAP. Caffeine citrate is also started to stimulate his respiratory effort. Because of a persistent heart murmur, an echocardiogram is performed which reveals a moderate to large patent ductus arteriosus with normal cardiac anatomy and function. He is not treated for this initially since he is not exhibiting signs of congestive heart failure. Phototherapy is also started for a serum bilirubin of 12 mg/dl. A head ultrasound, done at one week of age, reveals bilateral grade I-II intraventricular hemorrhages. He continues on parenteral nutrition but his feedings had to be discontinued due to abdominal distention and the presence of excessive residual breast milk noted in a gastric aspirate obtained just prior to his next feeding. By DOL 28, the infant, now 34 weeks adjusted age, is receiving full enteral feedings of breast milk and is occasionally breast fed by his mother. A routine eye exam is performed to screen for retinopathy of prematurity. He is found to have incomplete retinal vascularization to Zone 3 in both eyes. The ophthalmologist recommends follow-up in 2-3 weeks. His hemoglobin level is 10 g/dL and he is started on supplemental iron.

Prematurity is defined as birth prior to 37 completed weeks of gestation. Although, the rate of premature birth appears to vary by geographic region, the reported incidence varies between 6 and 10%. Despite significant improvements in perinatal care, there has not been a concomitant reduction in the rate of premature births in developed countries.

Prematurity and its associated problems are major contributors to the morbidity and mortality in the first year of life (which is reflected in the infant mortality rate).

Neonatal transition is the process involved in physiologic adaptation of the fetus to extrauterine life. Premature babies are at higher risk for slower transition to neonatal life due to immaturity of organ systems and lack of body mass. Premature (also called preterm) infants generally do not tolerate labor as well as term infants. This leads to a higher incidence of low Apgar scores and need for resuscitation in the delivery room.

Preterm infants have significant problems related to thermoregulation. Significant thermal stress may occur as they transition at birth from the in-utero fluid-filled environment supported by mother to the relatively cool air-filled environment of the delivery room. This can be avoided by providing exogenous heat with a radiant warmer during transition and minimizing heat loss by drying them quickly (evaporation of amniotic fluid on the skin is a potential cause of significant heat loss).

These infants are at risk for hypoglycemia because of limited glycogen stores and relatively immature glucose homeostatic mechanisms. It is important, therefore, to provide them with either a constant infusion of glucose solution intravenously, or early adequate enteral nutrition or both, depending on the baby's gestational age and degree of illness.

Respiratory problems are among the most common and important conditions related to prematurity. The immaturity of surfactant systems leads to respiratory distress syndrome (RDS).

Another common factor leading to respiratory difficulties is the relative compliance of the total respiratory system (chest wall, lung parenchyma and airways). Since the bony thorax that assists in the process of respiration is not fully developed (abnormally increased compliance) and the lung is often surfactant deficient (abnormally decreased compliance), the premature infant has increased work of breathing to maintain adequate functional residual capacity and tidal volume. This may lead to fatigue and respiratory failure in the smallest of infants. This problem often necessitates either endotracheal intubation and mechanical ventilation, or continuous positive pressure support to the airways and chest wall in the form of nasal CPAP via nasal prongs.

An additional factor is the incomplete development of the lungs (respiratory immaturity or immature lung disease). Alveolar development is not complete until several years of life. Immature lungs are at increased risk for long term injury. Some of the risk factors contributing to this injury include positive pressure/ventilator support (barotrauma), oxygen (oxygen toxicity), infections, and aspiration.

The gastrointestinal tract, especially with respect to the digestive enzymes and absorptive surfaces, is relatively well developed in premature infants. This is in contrast to the external muscular layer and neural control which is relatively less developed. Considering these factors, the inability of the GI tract to fully support the nutritional needs of the premature infant is related to volume (the total volume capacity of the system is low) and peristalsis (incomplete development of the neuromuscular components of the GI tract). The caloric intake required for the preterm infant to approach intrauterine growth rates is in the range of 120 to 150 Kcal/kg/d. These values are typically met by the 7th to 10th DOL Typically, a combination of enteral feeding and parenteral nutrition is necessary to achieve nutritional goals. Enteral feedings are often started at volumes of 10-20 cc/kg/d and advanced daily at increments of the same value. Thus, the majority of premature infants are at total enteral feedings within the first three weeks of life. Enteral feeds may consist of either with breast milk (ideally) or commercially available premature infant formula when breast milk is not available or contraindicated. Parenteral nutrition is comprised of a mixture of dextrose (carbohydrates), amino acids (proteins) and intralipids (fat) along with electrolyte additives and multi-vitamin supplements. Electrolyte and other mineral requirements (calcium, phosphorus, iron, zinc etc.) are higher for preterm infants because the body stores for these are significantly lower (the fetus builds up body stores primarily in the third trimester of pregnancy). Specially prepared formulas for preterm infants also contain additional amounts of calcium, phosphorus, and vitamins.

Necrotizing enterocolitis is a unique GI disorder related to prematurity and characterized by inflammation and necrosis of the intestinal tract. The ileum, cecum, or colon may be involved. The etiology is multifactorial. Risk factors include systemic infection, rapid advance of enteral nutrition, decreased intestinal blood flow (relative ischemia), the presence of catheters in umbilical vessels, and poor gut motility. The pathology consists of pneumatosis intestinalis (air dissecting within the bowel wall) and areas of bowel wall necrosis, occasionally leading to frank perforation. Perforation presents clinically with pneumoperitoneum, peritonitis, abdominal wall discoloration, and/or portal venous air. Management of this condition is primarily directed towards providing gut rest (NPO status), medical supportive measures (respiratory support, parenteral nutrition, intravascular volume, antibiotics), and surgical management in the case of perforation. Infants with NEC are at increased risk for intestinal strictures later in life.

Premature infants are not able to regulate their body temperatures as well as term infants. Factors that contribute to this problem are immaturity of the hypothalamic regulatory center, lack of subcutaneous fat (insulation shield), lack of brown fat (allows for thermogenesis in adverse climatic environmental conditions) and a relatively large body surface area to body mass ratio.

Typically, temperature control is maintained by providing an external heat source (radiant warmers or incubators/isolettes). These sources are set to provide heat to maintain a neutral thermal environment. In this environment, the infant has minimal energy expenditure to maintain core body temperature.

The majority of premature infants are able to regulate their body temperatures by a post conceptional age of 34 weeks. However, they remain at continued risk for poor thermal regulation at the extremes of environmental temperature. Parents should be appropriately counseled and encouraged to avoid subjecting their infant to temperature extremes.

The occurrence of physiologic jaundice in otherwise healthy term newborn infants is well recognized. Similar factors are associated with jaundice in the premature infant. These factors include a larger red cell mass at birth, shorter red cell half life, immaturity of liver enzyme systems, and poor gut motility promoting increased enterohepatic circulation. In contrast to term infants, physiologic jaundice in the premature infant tends to be visible earlier (1-2 days of age), peaks later (5-7 days of age) and may take up to two weeks to completely resolve. Whether premature infants are at greater risk for bilirubin neurotoxicity is unclear. It is well known that the potential for bilirubin neurotoxicity is increased in the presence of other associated medical conditions such as hemolysis, acidosis, respiratory failure, infections, and intraventricular hemorrhage. In the absence of such complications, there appears to be no evidence to suggest that bilirubin is more neurotoxic to the premature brain.

The most common cardiovascular problem in premature infants is the persistence of the ductus arteriosus. This vital in-utero communication pathway is programmed to close shortly after birth in term infants. This normal transition occurs less efficiently in the premature infant and the rate of spontaneous closure in inversely proportional to the degree of prematurity.

As the body systems go through other post-natal adaptations, the persistence of the ductus leads to significant problems including poor lung function related to increased pulmonary blood flow, ductal steal phenomenon leading to decreased systemic blood flow, and high output cardiac failure. Clinically, infants may present with a varied constellation of signs and symptoms that, in addition to a systolic murmur heard best at the left upper sternal border, include tachycardia, active precordium, bounding pulses, and cardiomegaly with pulmonary congestion on chest x-ray. Patent ductus arteriosus can be managed medically by using fluid restriction and indomethacin (prostaglandin inhibitor) therapy or surgically, by ductal ligation.

The germinal matrix is a unique vascular bed that is present in the region of the choroid plexus during development. Generally, this vascular system regresses completely by 32 weeks gestation. In infants born prior to 32 weeks gestation, this area is prone to vascular accidents that can lead to intraventricular hemorrhage. As is the general rule, the risk for more severe bleeding is inversely proportional to gestational age. One of the most important factors predisposing to hemorrhage in this area is hypoxic-ischemic injury. This type of intracranial hemorrhage tends to occur within the first week of life. Intraventricular hemorrhages are graded between 1 and 4 based on the extent of the hemorrhage, associated ventricular dilatation and associated parenchymal injury/infarction. Generally, Grade 1 and 2 lesions are compatible with near normal neurological outcomes while the long term neurological prognosis associated with Grade 3 and 4 lesions are more guarded.

Periventricular leukomalacia (PVL) is another manifestation of hypoxic-ischemic brain injury. It appears later than germinal matrix hemorrhages (GMH) described above. The lesions of periventricular leukomalacia are visualized as discrete cystic lesions in the periventricular white matter on cranial ultrasound. They appear primarily in the frontal and motor areas of the cerebral cortex.

All infants with the diagnosis of GMH or PVL need close neurodevelopmental follow up. They may need an early intervention program as deficits are identified. With timely developmental intervention, there is evidence that neurodevelopmental outcomes can be improved.

Apnea of prematurity is another physiologic entity that can complicate the clinical course of premature infants, especially those <34 weeks gestation. It is, in large part, related to the immaturity of the central respiratory center. By definition, apnea is the cessation of air flow/exchange. Apnea is often associated with bradycardia and hypoxemia. The majority of apnea events in premature infants are typically mixed (central and obstructive) in origin. The airway obstruction is usually the result of upper airway collapse or laryngeal closure. The response of the respiratory system to chemical stimuli (the primary process by which the respiratory center controls respirations) can be modulated by methylxanthines. The most commonly used drug to treat apnea of prematurity (AOP) is caffeine. This drug has been shown to reduce the severity and frequency of central apnea and periodic breathing in premature infants. In addition, caffeine toxicity is rare.

Retinal vascularization is incomplete until the completion of 32 weeks gestation. Thus, for infants born prior to this gestation, there is a risk of abnormal vascularization of the retina leading to retinopathy of prematurity (ROP). This is a disorder of angiogenesis that could potentially lead to blindness secondary to retinal detachment. The classification of ROP is based both, on the severity of the vascular disease, and the zone of the retina that is affected. The American Academy of Pediatrics and the American Academy of Ophthalmologists have jointly recommended a schedule for screening high risk premature infants for this disorder. Later on in life, prematurely born infants are at higher risk for refractive errors and, therefore, need to be closely monitored. It is recommended that they have a comprehensive ophthalmologic examination at 6 months to one year of age.

Premature infants are at the same risk for developing anemia of infancy as are term infants. This physiologic process occurs generally between the ages of 6 to 12 weeks. In addition, premature infants are at higher risk for protracted anemia, because they are born with lower body iron stores. This situation is further compounded by significant phlebotomy losses in the neonatal period related to hospitalization after birth. Anemia of prematurity may at least partially be overcome by the use of erythropoietin, which is used to stimulate erythropoiesis. Nevertheless, it is important to replenish the body's iron stores and the provision of supplemental iron is critical until the hemoglobin levels reach normal values for age. In this respect, the iron supplementation during therapy should be at the levels used in the treatment of anemia at any other age (up to 6 mg/kg/d of elemental iron).

Premature infants are at higher risk for infections. This risk is multifactorial. The primary source of immunity for the neonate is passively derived antibodies from the mother and this tends to occur primarily in the third trimester. Thus, the relative amount of antibody transferred is affected by the duration of gestation. Additionally, a significant proportion of premature infants who are hospitalized in intensive care units, require interventions such as IV therapy, and placement of central vascular catheters for providing nutrition, and invasive monitoring. All of these factors contribute to the increased risk of infections in this population. Premature infants present with nonspecific signs and symptoms of infection. This mandates close monitoring for infectious complications, both during hospitalization, in the immediate neonatal period, and in subsequent months during the first year of life.

Given their propensity for infections, the American Academy of Pediatrics recommends that all childhood immunizations be administered to premature infants at the appropriate chronological age. The only exception to this rule is the hepatitis B immunization, which should be initiated only after the infant's weight exceeds 2 kg. Despite lower titers of antibody response in these infants, there is no recommendation for additional doses of specific immunizations.

Passive prophylaxis for respiratory syncytial virus (RSV) infection is currently recommended during the cooler winter months for certain premature infants at highest risk for serious complications from RSV. These guidelines are evolving. The most current recommendation is published in the Red Book 2003 of the American Academy of Pediatrics. These infants will also benefit from receiving influenza immunization at 6 months chronological age during the cooler winter months (3).

The premature infant is ready for discharge when he/she is able to fulfill the following criteria: 1) ability to appropriately regulate their temperature without the need for technological support, 2) ability to ingest adequate calories to achieve consistent growth, and 3) to have demonstrated other parameters of global physiologic stability (the absence of clinically significant apnea, bradycardia, or hypoxemia). In addition, and most importantly, it is critical that the parents/caregivers feel comfortable with the care of the infant in the home environment. One of the issues that may alleviate some of the parental anxiety is training in infant CPR. Thus, the process of discharge of the infant is a continuum that begins several days to weeks prior to the actual discharge of the infant. Many of these infants will have additional needs and it is important that all of these needs and appropriate community resources are identified prior to discharge. At the time of discharge, the routine mandated screening for hearing and metabolic diseases should be completed with the results forwarded to the primary care physician.

The long term outcome of premature infants is inversely related to gestational age (better outcomes in older infants), and directly related to the clinical course in the neonatal period, and the associated morbidities and diagnoses during their hospitalization. In general, these infants need close neurodevelopmental monitoring and early interventions for identified problems. They are at increased risk for repeated hospitalization for various residual problems of prematurity such as bronchopulmonary dysplasia, failure to thrive, and feeding problems. Developmental outcome is also related to the home environment and the ability of the family to properly nurture the infant. Unfortunately, the stress associated with parenting a high-risk infant often leads to dysfunctional family dynamics. In addition, these infants are frequently born into families who are already high-risk. On a positive note, if an optimal nurturing environment is provided, there is evidence to suggest that it can result in a significant improvement in overall long term outcome.

Questions

1. True/False: Morbidity associated with prematurity is a significant contributor to the infant mortality rate.

2. Strategies to reduce thermal stress at birth should include (mark all correct answers):
    a. Keeping the delivery room warm and performing the stabilization under a preheated radiant warmer.
    b. Drying the infant and then wrapping them up with the same blanket.
    c. In a stable premature infant allowing skin to skin bonding with the mother.

3. Premature infants are at higher risk for hypoglycemia because (choose one):
    a. They are born with adequate glycogen stores but have immature homeostatic mechanisms to mobilize glucose.
    b. They are born with inadequate glycogen stores but have mature homeostatic mechanisms to mobilize glucose.
    c. They are born with inadequate glycogen stores and have immature homeostatic mechanisms to mobilize glucose.

4. Respiratory Problems in premature infants may be secondary to (choose one):
    a. Surfactant deficiency
    b. Increased chest wall compliance
    c. Incomplete alveolar development
    d. All of the above.

5. Feeding difficulties in premature infants are usually secondary to (choose one):
    a. Immature development of the intestinal enzyme systems.
    b. Immature neuromuscular development of the intestinal tract.

6. In contrast to term infants, the following statements are true regarding physiologic jaundice in the premature infant in the neonatal period (choose one):
    a. Has its onset later, reaches its peak later and has slower resolution.
    b. Has its onset earlier, peaks earlier and has earlier resolution.
    c. Has its onset earlier, peaks later and has slower resolution.

7. The following statements regarding the persistence of ductus arteriosus are true in the premature infant (choose one):
    a. Is one of the most common cardiovascular dysfunction.
    b. May be asymptomatic and spontaneously resolve in many.
    c. Can be treated with medications.
    d. All of the above.

8. Hypoxic-Ischemic brain injury can lead to (choose one):
    a. Germinal matrix hemorrhage/intraventricular hemorrhage
    b. Periventricular leukomalacia
    c. Both
    d. None

9. Apnea events in premature infants are usually (choose one):
    a. Central because of immaturity of the brain respiratory center.
    b. Obstructive secondary to collapse of the upper airway structures and closure of the glottis.
    c. Neither a or b.
    d. Both a and b.

10. In premature infants, routine immunizations should be (choose one):
    a. Administered at a post-conceptual age of two months.
    b. Administered at a post-natal age of two months.

11. True/False: The weight of the premature infant is an absolute criterion for discharge from the hospital.

Related x-rays

Newborn radiographs: Available online at: www.hawaii.edu/medicine/pediatrics/neoxray/neoxray.html

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Answers to questions

1.true, 2.a,c, 3c, 4.d, 5.b, 6.c, 7.d, 8.c, 9.d, 10.b, 11.false

Chapter III.6. Respiratory Distress in the Newborn

Daniel T. Murai, MD

A 2 hour old, 38 week gestation, 3 kg male infant was born to a 25 year old G1P1 A+, VDRL negative, Hepatitis B negative, GBS unscreened, Rubella immune, woman who had an uncomplicated pregnancy, labor and delivery. Apgar scores were 9/9. He was sent to the newborn nursery. He breast fed 1 hour ago without concerns. He now presents with respiratory distress.

Exam: VS T 37, HR 160, RR 80, BP 60/35 (mean 45), oxygen saturation 95% in 2 L/min oxygen via mask. Wt 3kg (50%), Lt 48cm (50%), HC 33.5 cm (50%). He is a term male with obvious respiratory distress and tachypnea. Skin is pale and pink without petechiae, ecchymoses, or lesions. His head is normocephalic with molding. His anterior fontanel is flat. His face is symmetrical with normal palpebral fissures, normal red reflexes, patent nares, normal ears, no clefts, and no neck masses. His chest is symmetric with equal and clear breath sounds. Mild to moderate chest retractions are present. Heart is regular with a normal S1, split S2, and no murmurs. His pulses are normal. His abdomen is soft and round with normal bowel sounds, no masses and no organomegaly. He has normal male genitalia with descended testes. His hips and anus are normal. He has mild hypotonia.

Laboratory results: CBC: WBC 15,000, 8% bands, 50% segs, 40% lymphs, 2% monos, Hct 55%, Plt 250,000. No toxic granulations or vacuoles of the neutrophils are noted. ABG: pH 7.35, PCO2 55 torr, PO2 70 torr, BE -7 in a 30% oxygen hood. CXR: 10 ribs of inflation, streaky linear perihilar densities, and small scattered patchy densities bilaterally.

Over the next several hours, the infant develops progressively more distress and a greater oxygen requirement. He is sent to the newborn special care nursery with worsening tachypnea (RR 90), more retractions and grunting. He is now in 50% O2 by hood.

What is your differential diagnoses? How would you manage this infant?

This chapter will cover the common problems which cause respiratory distress in the newborn within the first week of life. Based on the clinical presentation, onset and gestational age, the most likely diagnosis can be determined.

Respiratory distress is one of the most common presenting problems of newborns. The constellation of signs and symptoms can be the result of pulmonary, cardiac, metabolic, infectious, renal, gastroenterological and neurologic pathologic processes. Newborns with disorders involving any one of these organ systems may present with varying degrees of tachypnea, retractions, grunting, cyanosis, lethargy and tachycardia. Given the similar presentations, the circumstances of the newborn's birth provide important clues to the diagnosis.

Transient tachypnea of the newborn (TTN) is the most common respiratory disorder of the newborn. These infants are usually full term or slightly preterm. They are not at risk for other illnesses. Some infants are delivered by cesarean section; some without labor. The most significant discriminatory findings are the onset of the illness and the degree of distress exhibited by the infant. Typically, the infant becomes tachypneic immediately after birth and has mild respiratory distress. They are neurologically normal. If followed closely, infants remain stable for several hours and/or begin to improve. The chest radiographs reveal hyperinflation with clear lung parenchyma except

for perihilar linear densities and fluid in the fissures. There should be no areas of consolidation . The pathophysiological mechanism is the delayed resorption of fetal lung fluid which eventually clears over the next several hours to days. A worsening clinical picture should suggest another diagnosis. Treatment is generally close observation and symptomatic care. Low flow supplemental oxygen may be necessary for several hours.

Meconium in the amniotic fluid occurs in approximately 20% of pregnancies. As a consequence, meconium aspiration is considered to be a relatively common event. Other substances such as blood or amniotic fluid can also be aspirated. Infants with this disorder typically have symptoms similar to infants with TTN, but the presentation may suggest a more severe condition. In addition, while many infants have the onset of symptoms at birth, some infants have an asymptomatic period of several hours before respiratory distress becomes apparent. Infants with aspiration syndromes may require more oxygen, and have greater degrees of tachypnea, retractions and lethargy. The arterial blood gases may reveal more acidosis, hypercapnia and hypoxemia than in infants with TTN. The chest radiographs vary between that of TTN with hyperinflation and perihilar infiltrates to significant heterogeneous lung disease with hyperinflated and hypoinflated areas, patchy and linear infiltrates and atelectasis.

The pathophysiologic mechanism is the obstruction of large and small airways with the aspirated material (meconium, blood, amniotic fluid contents). Pulmonary hypertension may be develop when meconium aspiration occurs in conjunction with varying degrees of in utero asphyxia. Pulmonary hypertension, which often results from hypertrophic pulmonary vascular muscular tissue, is a severe condition characterized by cyanosis from right to left shunting across the atrial septum and patent ductus arteriosus. As the disease process progresses, the symptoms and severity of hypoxemia increase over the subsequent hours. While TTN is in the differential diagnoses initially, this progression should alert the clinician to another diagnosis such as an aspiration syndrome, pulmonary hypertension or infection. Treatment may include supplemental oxygen, mechanical ventilation and specific treatment for pulmonary hypertension, which includes high supplemental oxygen, high frequency mechanical ventilation, inhaled nitric oxide therapy and in the most severe cases, extracorporeal membrane oxygenation therapy (ECMO).

The duration of distress with mild to moderate aspiration syndromes is from several hours to days. Aspiration can occur in utero or during the intrapartum period as well as during the early postpartum period. Since meconium aspiration is the most common problem, much effort has been made over the last 30 years to prevent this disease by reducing intrapartum and postpartum aspiration. Thorough suctioning of the oropharynx with a large bore catheter upon the delivery of the head is typically performed by the obstetrician. The pediatrician, needs to assess the quality of the meconium (thin, moderate or thick) and the state of the newborn before determining what is needed after birth. A large randomized trial has confirmed that aggressive intubation is not necessary for most infants with meconium in the amniotic fluid. The recommendations provided by the NRP (Neonatal Resuscitation Program) are to suction the oropharynx of all infants after the delivery of the head and to intubate and suction the trachea of any infant with meconium in the amniotic fluid, if the infant is depressed (weak. respiratory effort, hypotonia and/or bradycardia).

The sudden onset of significant respiratory distress should raise the possibility of an air leak syndrome. The most common air leak syndromes are pneumomediastinum, pneumothorax and pneumopericardium. In addition to respiratory distress, a severe air leak condition may cause hypotension (due to decreases in cardiac output), muffled heart tones, abdominal distention, asymmetric chest shape and deviation of the cardiac sounds. Chest radiographs are diagnostic with free air in the hemithorax and a visible edge of the collapsed lung. If under tension (i.e., a tension pneumothorax), clinical deterioration will be rapid, the mediastinum will be deviated to the opposite (contralateral) side and the ipsilateral diaphragm will be depressed. The elevation of the thymus with a sail or bat wing sign suggests a pneumomediastinum. The heart is outlined with a halo of air in a pneumopericardium. Hypotension and bradycardia occur rapidly in a tension pneumothorax or pneumopericardium (cardiac dysfunction is due to reduced venous return due to compression of the heart and mediastinal vascular structures). The air leak syndrome known as pulmonary interstitial emphysema (PIE) is usually observed as a consequence of mechanical ventilation in an infant with severe respiratory distress syndrome.

Treatment of significant air leak syndromes requires immediate air evacuation (thoracentesis or pericardiocentesis) with a needle or small catheter, followed by chest or pericardial tube insertion. Pneumomediastinum does not require drainage. In cases other than a bronchopleural fistula, the air leak will usually seal within a few days.

Respiratory distress syndrome (RDS) is the most common disorder of the premature infant. Most infants are less than 34 weeks gestation and the incidence and severity increase with decreasing gestation age. These premature infants have progressively more severe respiratory distress after birth. The classic findings of cyanosis, grunting, nasal flaring, intercostal and subcostal retractions and tachypnea are present. The chest radiograph reveals decreased lung inflation with diffuse symmetrical reticulogranular (ground glass appearance) lung fields and air bronchograms. Oxygen requirements progressively increase over the first few hours after birth. The presence of apnea suggests severe disease accompanied by refractory hypoxemia and acidosis.

While the lung's structural immaturity contributes to the pulmonary dysfunction, the major reason for this disorder is surfactant deficiency. Without surfactant, the surface tension of the alveolar sacs is high, leading to an increased tendency of the alveoli to collapse. Laplace's law describes the behavior of the alveoli without surfactant. This relationship states that as the radius of the air filled alveolus decreases, the pressure within the alveolus increases. This increased pressure requires an equivalent external opposing pressure to keep the alveolus inflated. Without the opposing pressure, the gas under this pressure is forced out of the alveolus. If the alveolus is connected to an adjacent alveolus with a larger radius, air will preferentially inflate the larger alveolus and ultimately collapse the smaller alveolus. This leads to the network of air-filled alveoli juxtaposed to atelectatic alveoli and creates the reticulogranular pattern (ground glass appearance) of the lung. The air bronchograms are created by atelectatic alveoli outlining the adjacent rigidly distended airways. Air filled right and left mainstem bronchi are not visible if they are superimposed over air filled lungs, but when they are superimposed over partially collapsed, fluid filled lungs (as in RDS), the air filled bronchi are visible as air bronchograms. Grunting is the infant's attempt to maintain the pressures and gas volume within the lung by causing expiratory braking using the vocal cords (the glottis is partially closed during exhalation to maintain alveolar distending pressure during exhalation). Surfactant reverses this process. The phospholipids and surfactant related proteins, contained in surfactant, spread along the air liquid interface to decrease alveolar surface tension. Therefore the pressure required to keep the alveoli inflated is lower. Furthermore, the surfactant molecules contribute to the larger alveoli developing a higher surface tension during inspiration and a lower surface tension (as the alveoli deflate) during expiration when the surfactant molecules become more compact along the air liquid interface.

The treatment of RDS generally includes positive pressure ventilation and artificial surfactant replacement. The first purely synthetic surfactant is no longer available. Today, several types of animal based surfactants have been approved for clinical use. After endotracheal intubation, surfactant suspension is administered through the endotracheal (ET) tube and the infant is supported, until extubation is possible, with positive pressure ventilation and continuous positive airway pressure (CPAP) therapy as needed. High frequency ventilation has been shown to improve the short term management of these infants.

Moderately premature infants (29 to 34 weeks gestation) are usually extubated within several days after treatment. However, extremely premature infants (23 to 28 weeks gestation) may continue to require positive pressure respiratory support for several weeks. They are at high risk for bronchopulmonary dysplasia or chronic respiratory insufficiency of the premature. Bronchopulmonary dysplasia is the chronic lung disease consequence of early acute lung disease and/or lung immaturity of the premature infant. Chronic respiratory insufficiency of the premature develops despite early improvement after surfactant therapy and mechanical ventilation.

Infectious pneumonia in newborns is relatively rare. However, premature infants have at least a 10 fold increased incidence of infections when compared to term infants. Mothers with intrapartum fever and prolonged rupture of membranes (>18-24 hours) have a greater risk of transmitting infections to their infants. This risk can be reduced by administering intrapartum antibiotics for mothers with high risk pregnancies or women who are group B Streptococcus (GBS) carriers. However, the use of ampicillin for the GBS infections has increased the incidence of ampicillin resistant coliform infections. The most common bacterial organisms which infect neonates are the GBS, coliforms (E. coli being the most common member of this group), and Listeria monocytogenes. Infected infants present either immediately after birth with respiratory distress or they may present after several hours of an asymptomatic period. The degree of respiratory distress initially may mimic any respiratory disorder. Infants may have fevers or become hypothermic. The symptoms progressively increase in severity and if not treated may lead to shock, DIC and death. Due to the serious consequences associated with delays in treatment for infections, many infants with non-infectious conditions are evaluated and empirically treated with antibiotics for this possibility. The chest radiographs may resemble RDS (with reticulogranular infiltrates and air bronchograms), TTN or aspiration syndromes (with linear or patchy densities). It is unusual to have lobar consolidation from infection in the newborn. A term infant with RDS should be considered to have pneumonia until proven otherwise. The CBC may reveal either a leukocytosis or leukopenia. A left shift with greater than 20% band forms of the total neutrophils is suggestive of infection as are neutrophilic vacuoles and toxic granulation. Platelet counts may be normal or decreased. In severe cases, a coagulopathy with elevated PT and PTT and depressed fibrinogen levels may be present. The gold standard still remains the blood culture or culture of lung and tracheal secretions. Treatment with an aminoglycoside and penicillin is standard to treat for the common organisms. Supportive care may include mechanical ventilation, supplemental oxygen, inotropic agents for hypotension and nitric oxide for infection associated pulmonary hypertension. The mortality from infections has decreased from 50% to 20% with more aggressive intensive care.

Some congenital malformations of the cardiopulmonary system will be addressed here. The first is the infant with cyanotic heart disease. Most infants with transposition of the great arteries, tetralogy of Fallot and hypoplastic right and left heart syndromes, will present in the newborn period. Most infants with cyanotic heart disease typically have a paucity of respiratory distress symptoms except for cyanosis or duskiness. A murmur is usually present, but may be absent. Typically the chest radiograph reveals a normal sized heart or cardiomegaly with clear lung fields and decreased vascular markings (due to diminished pulmonary blood flow). When the infant develops respiratory symptoms, it is usually from severe hypoxemia or acidosis. The infant who is cyanotic with respiratory distress and does not respond to supplemental oxygen (i.e., their oxygen saturation does not improve significantly when given supplemental oxygen). Infants with both cyanosis and respiratory distress may have chest radiographs typical of pulmonary disease. The hyperoxy test (measuring the arterial pO2 while the infant is breathing 100% oxygen) is helpful in distinguishing cyanotic heart disease from severe respiratory disease. The echocardiogram is also diagnostic and will distinguish between cyanotic heart disease and persistent pulmonary hypertension.

Therapy for cyanotic heart disease consists of medical support until definitive surgical repair can take place. In many instances, patency of the ductus arteriosus is necessary to maintain mixing of pulmonary and systemic circulations. This is accomplished with an intravenous infusion of prostaglandin E1 infusions. Later, an artificial shunt is created from the aorta to the pulmonary arteries. Moderate oxygen supplementation to keep oxygen saturations approximately 80% or higher and mild acidosis to maintain a fetal type circulation is attempted to preserve pulmonary function. Multistaged open heart surgery may be necessary for most complex cyanotic heart diseases.

Structural abnormalities of the pulmonary system may also cause respiratory distress. Infants with congenital diaphragmatic hernia frequently present in the immediate newborn period with respiratory distress and refractory cyanosis. The abdomen is scaphoid since the intestines are in the thorax. Bowel sounds are heard over the chest if air enters the intestines from spontaneous breathing or mask valve ventilation. The chest radiograph reveals a bowel gas pattern typically in the left hemithorax with a mediastinal shift to the right. The heart compresses the right lung which may also be hypoinflated or hypoplastic. Surgery to remove the bowel from the thorax and close the diaphragmatic defect is necessary after the infant has been stabilized. High frequency ventilation and nitric oxide therapy are used to treat the bilateral hypoplastic lungs. The hypoplastic lungs develop excessive and abnormal musculature of the pulmonary vessels which lead to pulmonary hypertension. In the most severe cases, extracorporeal membrane oxygenation (ECMO) therapy is used to support the cardiopulmonary failure. However, despite aggressive treatment, approximately 50% of the infants with this condition do not survive. Lung volumes may reach normal values, but there is a persistence of decreased number of alveoli (emphysema). Please refer to the focused chapter on congenital diaphragmatic hernia.

In summary, the term infant with respiratory distress usually has transient tachypnea of the newborn. However, based on the time of onset and the progression and severity of the symptoms, other causes of respiratory distress must be entertained. Premature infants usually have RDS, but must be considered to be at risk for infection. In the case presentation at the beginning of this chapter, the later onset of respiratory distress which increases in severity with time, suggests either aspiration or an infectious process. The unremarkable CBC makes a pneumonia less likely and possibly supports an aspiration syndrome; however the CBC may change with time. Empiric antibiotic therapy is indicated. Management is supportive and supplemental oxygen should be continued. A repeat arterial blood gas is indicated and if the pCO2 is elevate, then consider mechanical ventilation. If the chest radiographs suggest significant atelectasis or a further increase in FiO2 is required, either nasal CPAP (continuous positive airway pressure) or mechanical ventilation with positive pressures may enhance oxygenation.

Simplified summary of some of the major newborn respiratory conditions:

RDS:
Clinical factors: Prematurity
CXR: Ground glass appearance

TTN:
Clinical factors: Short labor, C-section delivery
CXR: Fluid in the fissures, central/perihilar congestion

Meconium aspiration:
Clinical factors: Meconium in amniotic fluid
CXR: Infiltrates

Pneumonia:
Clinical factors: Prolonged rupture of membranes, maternal GBS, prematurity.
CXR: Infiltrates or hazy lungs (may be identical to RDS).

Pneumothorax:
Clinical factors: Sudden deterioration, often while on positive pressure ventilation.
CXR: Collapsed lung, free air in the hemithorax.

Cyanotic congenital heart disease:
Clinical factors: Heart murmur, persistent hypoxia despite supplemental oxygen.
CXR: Hypoperfused lungs (lungs appear darker). CXR is often normal.

Questions
1. What is the most common cause of respiratory distress in newborns?
2. When is the onset of symptoms for transient tachypnea of the newborn and how might this help distinguish TTN from other disorders?
3. Aspiration syndromes can be caused by what types of materials?
4. The sudden onset of significant respiratory distress and hypotension should suggest what respiratory disorder?
5. Respiratory distress syndrome of the premature infant is caused by what deficiency? What is the radiographic manifestation of this deficiency?
6. What organisms commonly cause newborn pneumonia?
7. What disorder would you consider in a cyanotic infant without respiratory distress?

Related x-rays
Newborn radiographs: Available online at: www.hawaii.edu/medicine/pediatrics/neoxray/neoxray.html

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Answers to questions
1. TTN
2. TTN symptoms occur soon after birth. Later onset of symptoms should suggest other disorders.
3. Meconium, blood, amniotic fluid.
4. Air leaks such as a tension pneumothorax.

5. Surfactant deficiency, which causes some alveoli to collapse next to alveoli which are emphysematous. Some atelectatic alveoli are adjacent to rigid bronchi. These conditions lead to a reticulogranular infiltrate (ground glass) and air bronchogram pattern on the chest radiograph.
6. Group B Streptococcus, gram negative rod organisms (usually E. coli) and Listeria monocytogenes.
7. Cyanotic congenital heart disease.

Chapter III.7. Cyanosis in Newborns
Kenneth Ash, MD

A 5 hour old male newborn infant was born at 39 weeks gestation via normal vaginal delivery to a 23 year old G2 P2 O+ mother with unremarkable prenatal serology studies. Apgar scores were 8 and 9 at 1 and 5 minutes. His initial physical exam was normal. He stayed in mother's room and breastfed shortly after delivery. At 5 hours of age, with the second feeding, the baby appears tachypneic and cyanotic, and he is therefore taken to the nursery for further evaluation.

Exam: VS T 37.0, HR 145, RR 78, BP 67/38, oxygen saturation 82% in room air. Length 53 cm (50%ile), weight 3.7 kg (50%ile), HC 34 cm (50%ile). He is an alert active, nondysmorphic and mildly cyanotic term male. Tachypnea and mild nasal flaring are present. His heart is regular with a grade 2/6 systolic ejection murmur at the lower left sternal border. The precordium is quiet. Lungs are clear bilaterally. No hepatosplenomegaly is noted.

He is placed in an oxygen hood with a fraction of inspired oxygen (FiO2) of 0.5 (50%) with no appreciable rise in his oxygen saturation.

A chest radiograph is normal. A radial arterial blood gas shows pH 7.44, pCO2 35, paO2 34, bicarb 22 in FiO2 0.7 (70%) by hood. Echocardiography reveals D-transposition of the great vessels with a 5mm ventricular septal defect and patent ductus arteriosus. A prostaglandin E1 infusion is started. The infant is mechanically ventilated and subsequently transported to a pediatric cardiac surgical specialty center. An arterial switch procedure is performed successfully. He is discharged home 3 weeks later.

The newborn infant with cyanosis challenges the clinician to identify the cause and institute appropriate treatment. Although cardiorespiratory disorders dominate the differential diagnosis, hematologic and metabolic derangements and neuromuscular disorders should also be considered.

As with all neonatal conditions, diagnosis is aided by obtaining a thorough maternal and birth history. Clues to infant problems may be found in pregnancy screening tests such as maternal serum alpha-fetoprotein, a marker for fetal aneuploidy, or knowledge of pre-existing maternal medical conditions such as diabetes. Maternal medications should also be noted. Both diabetes and chromosomal abnormalities increase the likelihood of congenital heart malformations. Although fetal ultrasound may reveal congenital heart, lung, or CNS anomalies, major anomalies frequently escape prenatal detection (1). Maternal serologies and cultures identify newborns at risk for perinatal group B streptococcal pneumonia or intrauterine toxoplasmosis infection.

The progress of labor and delivery, as reflected in Apgar scoring and delivery room resuscitation, also provides valuable information. An intrapartum complication leading to the need for aggressive neonatal resuscitation suggests an acquired perinatal etiology for neonatal cyanosis as opposed to a congenital cardiac malformation. Fetal heart rate pattern abnormalities, meconium staining of the amniotic fluid, maternal fever or bleeding may suggest neonatal pneumonia, hypoxic-ischemic injury, meconium aspiration syndrome or persistent pulmonary hypertension.

Cyanosis is recognized by evaluation of the mucus membranes and tongue. Peripheral cyanosis (acrocyanosis) is a normal finding in newborns and does not indicate systemic desaturation. The nail beds are not the place to look in newborns. Pigmentation of the vermilion border and facial bruising may also masquerade as cyanosis. It is necessary to look in an infant's mouth to get a true assessment of oxygenation.

The prerequisite for recognition of cyanosis is thought to be 5 g/dL or more of desaturated hemoglobin. Infants who are both hypoxic and severely anemic may escape recognition because the amount of desaturated hemoglobin is below the level of detection. Likewise, the polycythemic infant with a normal oxygen saturation may appear cyanotic from peripheral sludging of desaturated red cells despite normal oxygen saturation.

Minor levels of desaturation may also escape visual detection. Infants with oxygen saturation in the mid 80's often appear pink, especially under the bright lights above radiant warmers, and are judged to have normal Apgar scores and transition assessments. Only later is the hypoxia detected with the investigation of ancillary signs such as tachypnea, tachycardia or other signs of distress.

In general, cyanosis associated with respiratory problems is accompanied by dyspnea, retractions and grunting, possibly leading to apnea. The quality and symmetry of breath sounds may suggest focal disorders such as pneumothorax and diaphragmatic hernia or more generalized ones such as respiratory distress syndrome. Cyanotic cardiac disease may produce only tachypnea or a more dramatic picture of respiratory distress if pulmonary circulatory overload is present.

Heart murmurs are common in neonates during perinatal transition. The systolic murmurs of a patent ductus arteriosus and tricuspid regurgitation are heard in normal neonates. More infrequently heard holosystolic or diastolic murmurs require definitive evaluation. Conversely, many serious cyanotic congenital heart malformations are not accompanied by murmurs. The quality of peripheral pulses should be noted. Generally weak pulses denote systemic hypoperfusion as in low volume states and decreased cardiac output. Decreased femoral pulses alone suggest coarctation of the aorta. Bounding pulses suggest a widened pulse pressure.

The association of cyanosis with dysmorphic features may provide diagnostic information. For example, Down syndrome (trisomy 21) as well as trisomy 18, trisomy 13 and Turner (XO) syndrome are associated with specific cardiac malformations. Colobomata (eye defects), choanal atresia, genital and ear anomalies appear with cardiac defects such as tetralogy of Fallot in the CHARGE association (Coloboma, Heart defects, Atresia choanae, Retardation of growth and development, Genitourinary problems, Ear abnormalities). Facial and limb deformation associated with oligohydramnios is associated with hypoplastic lungs and pulmonary hypertension leading to cyanosis (5).

The most common congenital heart lesions presenting with cyanosis in the newborn period are those of the hypoplastic right heart syndrome complex (pulmonary and tricuspid atresia) and transposition of the great vessels. The basic pathophysiologic mechanisms leading to hypoxemia are inadequate perfusion of the lungs or marked right-to-left shunting and admixture of desaturated venous blood in the systemic arterial circulation. The most common cardiac conditions seen in Hawaii are listed in the table below.

Table. Cyanotic Congenital Heart Disease in Hawaii 1986-1998 (2). N=264,833 births

Diagnosis	Number
Pulmonary Artery Atresia/Stenosis	407
Persistent Pulmonary Hypertension	187
Tetralogy of Fallot	105
Transposition of the Great Vessels	104
Pulmonary Valve Atresia/Stenosis	43
Tricuspid valve atresia/stenosis	38
Hypoplastic Left Heart	44
Truncus arteriosus	26
Total Anomalous Pulmonary Venous Return	22
Single Ventricle	17
Partial Anomalous Pulmonary Venous Return	12
Ebstein's Anomaly	9

Persistent pulmonary hypertension (PPHN) of the newborn mimics many signs and symptoms of structural heart disease, and the effort to distinguish the two is a common clinical challenge. PPHN (formerly called persistent fetal circulation) may be a primary problem with little antecedent history or more commonly an associated problem of primary pulmonary diseases such as meconium aspiration syndrome, congenital diaphragmatic hernia, respiratory distress syndrome and congenital heart disease.

The entire gamut of neonatal respiratory disorders may present with cyanosis. The chest x-ray and history in combination often suggest the diagnosis. Some of the more common conditions include respiratory distress syndrome, meconium aspiration syndrome, neonatal pneumonia, and pneumothorax. Less common conditions include congenital anomalies of the lungs such as congenital diaphragmatic hernia, tracheoesophageal fistula and pulmonary hypoplasia. Transient tachypnea of the newborn, a common neonatal respiratory disorder, generally is not accompanied by marked cyanosis.

Central nervous system dysfunction caused by hypoxic ischemic injury, seizures, intracranial hemorrhage, infection, or metabolic derangement such as hypoglycemia may lead to cyanosis. Severe neuromuscular diseases such as phrenic nerve palsy, Werdnig-Hoffmann disease, or neonatal botulism may affect respiratory function and lead to cyanosis (6).

Methemoglobinemia may produce a slate gray hue to the skin generally accompanied by low oxygen saturation and hypoxemia, although an arterial pO2 on a blood gas will be paradoxically normal (similar to carbon monoxide poisoning since methemoglobin similarly does not carry oxygen). Methemoglobinemia is associated with ingestion of toxic agents such as nitrites and congenital absence of methemoglobin reductase. An usual pattern of methemoglobinemia has also been described in infants with diarrheal disease of various etiologies including milk protein intolerance and infectious gastroenteritis accompanied by severe systemic acidosis (3,4).

Echocardiography with color-flow Doppler is the definitive test for cyanotic structural heart disease and PPHN. However, prior to obtaining a cardiology consultation and echocardiogram, the clinician may perform a number of other valuable tests to define the cause or mechanism of cyanosis.

An anteroposterior chest x-ray will identify pneumonia, pneumothorax or the intrathoracic bowel gas patterns characteristic of diaphragmatic hernia. The shape and size of the cardiac silhouette and prominence of the central pulmonary vessel may provide clues to cardiac pathology. The classic cardiac silhouettes of transposition of the great vessels ("egg on side"), total anomalous pulmonary venous return ("snowman" heart) and tetralogy of Fallot (boot-shape) are uncommon in the newborn period. The chest x-ray appearance of PPHN is variable: oligemic (hypoperfused) lung fields in the idiopathic variety, prominent infiltrates (if accompanied by meconium aspiration syndrome), or normal in some cases.

The hyperoxy test is a rapid bedside screen for cyanotic diseases that do not respond to supplemental oxygen. The patient is placed in a high concentration oxygen hood (FiO2 at or near 100%) and the paO2 or oxygen saturation by pulse oximetry is compared to the value in room air. A significant increase in oxygen saturation or paO2 suggests pulmonary pathology, whereas an insignificant change in oxygenation suggests the fixed right-to-left shunting of structural cyanotic congenital heart disease, PPHN or very severe pulmonary disease.

Two pulse oximeter probes placed simultaneously on an upper and lower extremity will give clues to right-to-left shunting across a patent ductus arteriosus. A higher oxygen saturation reading in the hand than the foot is classically seen in PPHN and interrupted aortic arch. Likewise, a marked differential in paO2 between blood drawn from an upper extremity artery and umbilical artery catheter or posterior tibial artery carries the same implication.

Laboratory studies such as arterial blood gases can also supply information on ventilation and acid base status. A methemoglobin level can be ordered if methemoglobinemia is suspected. A rapid bedside screen for methemoglobinemia is arterial blood which has a "chocolate" color which does not turn red after several minutes of exposure to room air or oxygen.

The CBC provides an index of hemoglobin level. Polycythemia may exaggerate or falsely mimic cyanosis, while anemia may mask it. The white count, differential, and platelet count provide clues to disorders associated with inflammation and coagulopathy such as sepsis. Blood glucose should be monitored, as hypoglycemia may be an accompanying factor or the inciting cause of cyanosis. Infants ill enough to be cyanotic may require blood transfusion either for stabilization or surgery.

Echocardiography provides the definitive answer in the majority of common congenital heart lesions and PPHN. Rarely is cardiac catheterization required, except in confusing cases of complex anatomy or instances of uncertainty. The diagnosis of PPHN rests primarily on the finding of normal cardiac anatomy and direct evidence of right-to-left or bidirectional shunting of blood on color-flow Doppler through the foramen ovale or ductus arteriosus. Elevated right ventricular systolic pressures estimated by regurgitant flow through the tricuspid valve, ventricular septal flattening or paradoxical wall motion suggest but do not define PPHN in the absence of demonstrable shunting (7).

Targeted treatment is dependent on accurate diagnosis and understanding of pathophysiology. Respiratory support with oxygen or mechanical ventilation is often required in cyanotic newborns. In most cases, oxygen supplementation is helpful if not vital. An

exception to this rule is in functionally univentricular hearts (as in hypoplastic left heart syndrome), in which cardiac output to the systemic versus pulmonary circulation is dependent on a balance of the relative resistance of each vascular bed. Oxygen, a potent pulmonary vasodilator, may increase pulmonary blood flow at the expense of systemic perfusion. In anomalous pulmonary venous return with obstruction, oxygen therapy may be particularly hazardous contributing to increasing pulmonary venous hypertension and clinical deterioration. However, in most pulmonary problems and PPHN, oxygen and ventilation are important aspects of supportive care. When a prostaglandin E1 infusion is used to maintain patency of the ductus arteriosus in ductal dependent lesions, apnea is a common side effect. Anticipation of this common complication and stabilization of the patient's airway and ready availability of ventilatory support can avoid deterioration especially in the transport setting. In transposition of the great vessels, timing and severity of presentation relates to the degree of right/left mixing. If there is a coexisting ventricular septal defect with adequate mixing, recognition may be delayed up to several weeks. However if a VSD is absent or mixing is inadequate, an emergency balloon atrial septostomy (Rashkind procedure) may be necessary prior to definitive repair (8).

Therapeutic use of nitric oxide, an endogenous regulator of vascular tone, has revolutionized the treatment of PPHN. Mortality from this condition, which at one time approached 50%, has improved in recent decades. Strategies for treatment have included aggressive oxygen use and hyperventilation to lower pulmonary vascular tone. When these approaches failed, extracorporeal membrane oxygenation (ECMO) was used as a successful rescue treatment. Multiple ECMO centers were established around the country in the 1980s. However with clinical trials of inhaled nitric oxide (iNO) in the 1990s and FDA approval of iNO in 1999, there has been a steady decrease in the use of ECMO in the United States (9).

Adequate support of cardiac function with inotropic agents such as dopamine, dobutamine, epinephrine, and milrinone infusions is extremely important in both PPHN and other cardiovascular diseases resulting in cyanosis. Red blood cell transfusion is commonly employed to support oxygen carrying and delivery capacity. Metabolic needs are addressed with provision of adequate glucose and nutritional support. Attention to fluid and electrolyte balance includes calcium maintenance for optimal cardiac performance. Acid-base derangement is addressed with attention to treatment of underlying disorders and the judicious use of sodium bicarbonate.

In the unusual event of cyanosis due to methemoglobinemia, methylene blue, an exogenous electron donor for NADPH-methemoglobin reductase, can be used in severe symptomatic cases. Methylene blue will be ineffective in babies with G6PD deficiency, because reduction of methylene blue requires an intact pentose phosphate pathway (10). Although methemoglobin is produced during iNO therapy for PPHN, concentrations are generally clinically insignificant.

Cardiac surgery techniques have improved to the point where palliative procedures such as systemic to pulmonary shunts have been largely replaced when possible by primary definitive repair in the newborn period. Examples are the arterial switch (Jatene) procedure for transposition of the great vessels and primary repair of anomalous pulmonary venous drainage and tetralogy of Fallot. Staged procedures are used for more complex lesions with unfavorable anatomy. Immediate outcome for the arterial switch procedure is 90-95% survival in the newborn period. The best outcomes for neonatal cardiac surgery are seen in pediatric cardiac centers with high volumes and skilled teams (8,11).

Questions

1. What are the 2 most common congenital heart diseases leading to cyanosis in the newborn period?

2. What therapies are used as a bridge to definitive therapy in cyanotic congenital heart disease?
   a. Prostaglandin E1 infusion
   b. Mechanical ventilation
   c. Inotropic agents
   d. All of the above

3. True/False: The definitive treatment for pulmonary hypertension of the newborn is surgical?

4. A 12 day old infant, exclusively fed cow's milk formula, presents to the ER appearing greyish/cyanotic. With 5L/minute oxygen by mask, his radial artery paO2 is 236 torr. His most likely diagnosis is:
   a. Tetralogy of Fallot
   b. Persistent Pulmonary Hypertension
   c. Methemoglobinemia
   d. Transposition of the Great Vessels

5. A 2 day old term infant previously thought to be well and about to be discharged from the nursery becomes acutely pale, slightly cyanotic, with weak femoral and brachial pulses. The congenital heart disease most likely to present in this manner is:
   a. Tetralogy of Fallot
   b. Hypoplastic Left Heart Syndrome
   c. Tricuspid Atresia
   d. Total Anomalous Pulmonary Venous Return

6. Name the four components of Tetralogy of Fallot. Of these four, which one most determines the severity of the cyanosis?

7. True/False: Because cardiac murmurs are uncommon in the newborn period, echocardiography should be performed on all newborns when a murmur is detected.

8. True/False: Cyanosis of the hands and feet of a newborn may be normal if the mucus membranes are pink.

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Answers to questions

1. Hypoplastic right heart syndrome/Pulmonary atresia (these two are part of a spectrum) and transposition of the great vessels.
2. d. All of the choices are correct.
3. False
4. c
5. b
6. Ventricular septal defect (VSD), overriding aorta, pulmonic stenosis, right ventricular hypertrophy. The severity of the pulmonic stenosis is the most important factor in determining the degree of cyanosis.
7. False.
8. True.

Chapter III.8. Neonatal Hypoglycemia
Joel Ruff, MD

This is a newborn infant male delivered to a 25 year old G5P3, A+ mother at 37 weeks gestation by C section (for non-reassuring fetal heart tones). The pregnancy is notable for an antenatal ultrasound diagnosis of cleft lip and palate. Maternal serologies are unremarkable and her prenatal glucose tolerance test is normal. At delivery, blow-by oxygen is given for about 2 minutes for poor color and respiratory effort. Apgar scores are 6 (-2 color, -1 tone, -1 respiratory effort) and 9 (-1 color) at one and five minutes, respectively.

Exam: Vital signs are normal. Oxygen saturation is 99% in room air. Weight is 3950 gms, height is 54 cm and head circumference is 37.5 cm (all >95th percentile for gestational age). The infant is active and jittery with an obvious left sided cleft lip and palate. Heart is regular without murmurs. Lungs are clear. Abdomen is soft, without masses or hepatosplenomegaly. The remainder of the initial exam is normal.

The infant is transferred to the term nursery for transitioning. A bedside glucose is obtained and the blood sugar is read as close to 0 mg/dl. A serum sample is then sent STAT to the lab. An IV is started and 8 ml (2 mg/kg) of 10% dextrose in water (D10W) is given IV. The infant is transferred to the intermediate nursery where a repeat blood sugar 30 minutes after the bolus is still <20 mg/dl. A second IV bolus of D10W is given. The earlier serum glucose sent to the lab, comes back at <2 mg/dl. IV D10 is infusing at 80 ml/kg/day, which is a glucose infusion rate of 5.6 mg/kg/min. A blood sugar obtained 30 minutes after a second bolus is 31 mg/dl. The fluid is changed to 12.5% dextrose (D12.5W), the maximum concentration that can run in a peripheral IV. A third glucose is still below 40 mg/dl and a third bolus is given. The D12.5W infusion is increased to 100 ml/kg/day, which is a glucose infusion rate of almost 9 mg/kg/minute, and the baby is offered some formula. The next blood glucose is 48 mg/dl. The infant requires 100 ml/kg/day of dextrose 12.5% for about 24 hours, and then is able to be slowly weaned off the IV fluids.

Neonatal hypoglycemia is a very common condition. The stated incidence is estimated at 1 to 5 per 1000 births, but it is significantly higher in certain subgroups, 8% in LGA (large for gestational age) infants and about 15% in SGA (small for gestational age) infants (i.e., those with intrauterine growth retardation) (1). Neonatal hypoglycemia can be easily treated in most cases if it is recognized, but untreated hypoglycemia can have serious consequences for the infant as glucose is the major substrate for energy in all organs and almost exclusively used for cerebral metabolism (1).

In the fetus, serum glucose levels are about 70% of those in the mother (i.e., baby's glucose is about 70, when mother's glucose is 100) and almost all of this comes from facilitated diffusion across the placenta. Stores of glycogen in the liver accumulate slowly through gestation with a marked increase during the last trimester.

After delivery, the maternal supply of glucose is interrupted. Fetal glycogen storage is temporarily inactivated and glycogen phosphorylase breaks down hepatic glycogen stores to supply glucose. A term infant is estimated to have only enough hepatic glycogen to support metabolic demands for about 10 hours without an exogenous energy source. At the same time, synthesis of enzymes involved in gluconeogenesis increases and catecholamine levels are high (stimulating the release of substrates in the form of free fatty acids and free amino acids). Blood glucose levels in all infants take a physiologic dip in the first 30 to 60 minutes of life and then increase to a stable level at about 1.5 to 3 hours after birth.

Since Van Creveld recognized that premature infants had lower levels of blood sugar than term infants in 1929 (2) and Hartmann and Jaudon defined groups of "mild," "moderate" and "extreme" hypoglycemia in 1937 (3), the concept of what level of hypoglycemia is physiologically significant has been evolving. Animal studies suggest that hypoglycemia causes brain injury via multiple mechanisms which include excess glutamate, an excitatory amino acid neurotransmitter, free fatty acid release and increased mitochondrial free radicals. Glutamate action on its main receptor, the N-methyl-D-aspartate (NMDA)-type glutamate receptor may transport excess sodium and calcium into neuronal cells and cause selective neuronal necrosis via multiple mechanisms. Although there is an understandable lack of controlled studies in human infant subjects, it is known that the neonatal brain is more tolerant of low blood sugars than the adult brain. Long term effects on cognition and development are difficult to define from a case report literature base. There is a lack of correlation between the glucose level alone and permanent neurodegeneration (4, 5).

Studies in humans, limited to follow up evaluations of infants with hypoglycemia, are complicated by confounding problems such as hypoxia or prematurity, non-uniform definitions of hypoglycemia and lack of control groups. Some studies show adverse neurodevelopmental outcomes and some do not. The article by Cornblath and Ichord (6) is an excellent review of the current state of the literature on this topic. Recently, new imaging modalities including positron emission tomography (PET) and magnetic resonance imaging (MRI) are being used to evaluate function and structure of infant brains affected by hypoglycemia. One study stated that the "prognostic value of these techniques remains still obscure" but the possibilities are exciting (7).

Practically, however, an operational threshold of hypoglycemia for evaluation and treatment needs to be available for the practitioner. It is important to realize that the definition of hypoglycemia may vary from patient to patient. A healthy term infant in no distress may tolerate 30 mg/dl well but a stressed, premature infant may be symptomatic at 50 mg/dl. Symptomatic and very low blood sugars (<20 mg/dl) deserve quick assessment and treatment.

Some infants deserve special attention because of their high risk of hypoglycemia (8,9,10). These include: 1) Infants of diabetic mothers many of whom are LGA, 2) All macrosomic (LGA) infants (mothers may have occult diabetes), 3) SGA, (i.e., intrauterine stressed) infants, 4) Stressed infants (i.e., difficult delivery, low Apgar <7 at five minutes), 5) Infants of mothers on tocolytics (terbutaline, ritodrine), oral hypoglycemics or propranolol within 72 hrs before delivery, 6) Premature infants (<37 weeks gestational age), 7) Postmature infants (>42 weeks gestational age).

Hypoglycemic newborn infants may present with a variety of symptoms or be entirely asymptomatic. Symptoms may include: apnea, jitteriness, exaggerated Moro, irritability, poor sucking or feeding, cyanosis, hypotonia, lethargy or coma, temperature instability, seizure, tachypnea (rare), heart rate abnormalities (slow or fast), abnormal cry or vomiting. Because these signs and symptoms are fairly nonspecific, the differential should include other entities such as sepsis, hypocalcemia or intracranial hemorrhage, as appropriate for the clinical setting (1,8).

The differential diagnosis of hypoglycemia is wide, but a few diagnoses make up the bulk of cases. A convenient way to consider the differential is to divide it into transient hypoglycemia or persistent/recurrent hypoglycemia. The latter is defined as requiring either parenteral glucose for more than 7 days or high IV glucose infusion rates (>12-16 mg/kg/min) (6,8).

Transient hypoglycemia can be due to maternal or neonatal conditions. Refer to the table below.

1. Maternal conditions causing transient hypoglycemia:
    a. Intrapartum glucose given at too high a rate to the mother.
    b. Drug treatment (terbutaline, ritodrine, propranolol, oral hypoglycemics).
    c. Intrauterine growth retardation (IUGR): placental insufficiency resulting in SGA infant.
    d. Diabetes in pregnancy (hyperinsulinism).

2. Neonatal conditions causing transient hypoglycemia:
    a. Failure to adapt to extrauterine life: "Transient developmental immaturity of critical metabolic pathways" (6).
    b. Birth asphyxia: Hypermetabolism following acute brain injury and/or energy metabolism shifting from aerobic to anaerobic pathways (exact mechanism unknown) (6,10).
    c. Infection: Hypoglycemia due to overwhelming sepsis. Intracranial infection may also be associated with hypoglycemia (6,10).
    d. Hyperviscosity: There is an inverse correlation with hematocrit and blood glucose levels (10) .
    e. Congenital heart disease: May be related to metabolic demands of congestive failure (10).
    f. Erythroblastosis fetalis: Previously reported to be associated with erythroblastosis fetalis from Rh incompatibility, which is uncommon today (10).
    g. Hypothermia: Increased calories expended to thermoregulate (6).
    h. Inadequate provision of calories.
    i. Other iatrogenic causes: Associated with exchange transfusion and/or low lying umbilical artery catheter which selectively perfuses the pancreas (T11-L1) with a high glucose solution resulting in hyperinsulinism (8, 10).
    j. Decreased glycogen stores: Associated with pre and postmature infants (8).

An endocrinology consult is indicated for persistent and/or recurrent hypoglycemia. Causes include hyperinsulinism, endocrine deficiency, inborn errors of metabolism and neurohypoglycemia (a rare condition in which the subject lacks a transport protein (GLUT1) that facilitates glucose transport across brain microvesicles) (10).

1. Hyperinsulinism conditions which cause persistent/recurrent hypoglycemia:
    a. Nesidioblastosis: A very rare condition in which the pancreas has beta cell hypertrophy. This condition is on a continuum with islet cell adenoma and usually requires subtotal or total pancreatectomy to treat (8,10).
    b. Beckwith-Wiedemann syndrome: Visceromegaly, macroglossia, hypoglycemia.

2. Endocrine deficiency conditions which cause persistent/recurrent hypoglycemia:
   a. Pituitary insufficiency: Associated with syndromes such as septo-optic dysplasia, craniofacial defects and anencephaly (the case patient had a cleft lip and palate which has been associated with patients who have pituitary insufficiency) (10). Deficiency of pituitary hormones such as growth hormone and ACTH, results in hypoglycemia.
   b. Cortisol deficiency/adrenal failure.
   c. Congenital glucagon deficiency.
   d. Epinephrine deficiency: Extremely rare (10).

3. Inborn errors of metabolism conditions which cause persistent/recurrent hypoglycemia (6):
   a. Carbohydrate metabolism: Galactosemia, glycogen storage disease, fructose intolerance.
   b. Amino acid metabolism: Maple syrup urine disease, propionicacidemia, methylmalonic aciduria, tyrosinemia, glutaric acidemia.
   c. Fatty acid metabolism: Carnitine metabolism defect, Acyl-CoA dehydrogenase defect.

Your first evaluation of such an infant should be of airway, breathing and circulation (ABCs). Sepsis may present with hypoglycemia. Most nurseries use a glucose oxidase/peroxidase chromogen test to do bedside determination of blood glucose (Chemstrip or others). This method is quick and fairly easy, but variability in the amount of blood on the strip or residual isopropyl alcohol on the baby's skin may affect readings. Values are given in a range (i.e., 20-40 mg/dl or 40-80 mg/dl). Estimates of sensitivity of this method are 85% but the false positive rate may be as high as 25% (1). The strips are less accurate in the lower ranges (40 mg/dl or less). Because these lower values are of greater clinical concern and because of the variability of reading these strips, these visual methods of estimating blood glucose have been replaced by more precise electronic bedside glucose measurement devices. A stat serum level should be sent to the lab to verify low glucose values. A complete blood count may be a helpful screen for infection and to evaluate the possibility of polycythemia (8). In the lab, plasma or serum is separated from the blood sample and the glucose concentration is measured on the plasma or serum. Thus, a "blood" glucose is really a serum or plasma glucose. The terms blood, serum and plasma glucose can be used interchangeably since they are numerically identical.

The goal of treatment is to establish normoglycemia, usually defined as a stable glucose value above 40 or 50 mg/dl. Definitions vary depending on the clinical situation. All symptomatic infants should be treated with intravenous glucose. Asymptomatic infants in the 20-40 mg/dl range may have a trial of oral feeding, but if the glucose fails to normalize, an IV glucose infusion should be started. Although dextrose 5% (D5W) oral solution is occasionally used for treatment, formula has the advantage of containing fats and proteins which are metabolized slowly and provide a more sustained level of substrates for glucose production (1). Blood glucose should be rechecked in 30-60 minutes after feeding.

For symptomatic infants or asymptomatic infants with severe hypoglycemia (<20 mg/dl), a small IV bolus of dextrose has been shown to raise blood sugar levels safely and more quickly to adequate levels than intravenous infusion alone. The usual bolus is 2 ml/kg of a dextrose 10% (D10W) solution given intravenously followed by a glucose infusion rate of 6 to 8 mg/kg/min. The first part of the infusion, i.e., the bolus is given as a dose of ml/kg, but the second part of the infusion is given in mg/kg/min. This makes it a more difficult conversion because the user must convert grams of glucose to ml, then they must convert ml per minute to ml/hour, since ml/hr is the unit used on IV pumps. A simplified formula for glucose infusion rate (in mg/kg/min) is:

Glucose infusion rate (GIR) = (dextrose%concentration X ml/kg/d) / 144

So if dextrose 10% is used at 80 ml/kg/day that gives us:

GIR = (10 x 80) / 144 = 800 / 144 = 5.6 mg/kg/min

A faster way to figure this out is to use one of the following formulas to achieve a glucose infusion rate of 7 mg/kg/minute.

D5W: IV rate (in ml/hr) = 8.4 X Body Wt (in kg)
D10W: IV rate (in ml/hr) = 4.2 X Body Wt (in kg)

For a 3 kg newborn infant, using D5W would result in an IV rate of 25 ml/hr, which results in 600 ml/day, or 200 cc/kg/day, which is too much. This is why D10W must be used instead. The D10W infusion rate using the above formula would still give 100 cc/kg/day.

The glucose utilization of healthy infants is 5 to 8 mg/kg/min so the above mimics the endogenous requirements. A healthy term infant typically requires only about 60 ml/kg/day of fluids (on the first day of life). In this case, the increased fluids are being used as a vehicle for adequate glucose administration. Giving 15 ml (1/2 ounce) of a standard 20 calorie per ounce formula provides roughly 1.1 gm of carbohydrate (plus protein and fat, which provides additional calories). A 15 ml IV bolus of D5W provides 0.75 grams of glucose, while 15 ml of D10W, provides 1.5 grams of glucose. Formula provides more glucose equivalent than D5W and about as much glucose equivalent as D10W.

What if the follow up glucose (which should be obtained 30-60 minutes after the infusion) is still low, as it was in the patient described above? The options include either increasing the IV rate or increasing the dextrose concentration (i.e., increasing the GIR). The next higher dextrose concentration that is readily available is D12.5W. Because of hypertonicity, peripheral veins cannot tolerate more than 12.5% dextrose. This means that an infant requiring a higher glucose concentration needs a central line. Some infants may require glucose infusion rates as high as 16-20 mg/kg/min, but any infant in this range needs further evaluation and an endocrinology consult.

If the plasma glucose cannot be raised by glucose infusion alone, other options include a trial of corticosteroids (hydrocortisone 5-15 mg/kg/day IV in 2-3 divided doses or prednisone 2 mg/kg/day by mouth). If this fails, other drugs that may be used to raise the plasma glucose include human growth hormone, diazoxide, glucagon or long acting synthetic somatostatin (octreotide) (8).

The first step in evaluating persistent/recurrent hypoglycemia is to obtain serum glucose, insulin, and ketone levels. If the ratio of insulin to glucose (I/G ratio) is >0.3, then the cause is hyperinsulinism. Ketones should be low or absent in hyperinsulinism (4). Ketones are normally generated in hypoglycemic states because the body breaks down fat to acetyl CoA and other ketone bodies, in an effort to generate more substrate for the Krebs cycle. However, in a hyperinsulin state, insulin stimulates lipid synthesis (the opposite of fat breakdown) and thus, ketone levels will be low or absent. Other labs that can be helpful in the diagnosis include growth hormone levels, serum cortisol, free fatty acids, free T4, TSH, uric acid, glucagon, lactate, alanine, amino acids, and somatomedins. Imaging of the pancreas, heart or brain may also be indicated (8).

If the patient is stable, the blood sugar is steady at 50 mg/dl or above, and a more serious condition is not suspected, the frequency of blood glucose measurements can be reduced to every 4 to 6 hours. The intravenous glucose infusion may be weaned after the glucose has been stable and in the normal range for 12-24 hours (1). Some clinicians prefer 2 to 3 days of stable blood sugars before weaning (10). The infusion should be weaned 10-20% every several hours. Enteral feedings may be started concurrently if the infant is otherwise stable and fluid overload is not a concern. Failure to wean should prompt the above evaluation.

Questions

1. True/False: The level of hypoglycemia resulting in serious sequelae is well defined by scientific studies.

2. The advantage of using formula over 5% dextrose water (oral) to feed a moderately hypoglycemic term infant is:
   a. More sustained rise in blood sugar.
   b. A much faster rise in blood sugar than with dextrose 5% oral.
   c. Infants less than 3 hours old cannot take formula yet.
   d. One ounce of standard formula is equivalent gm per gm to a 2 ml/kg intravenous bolus of 5% dextrose.

3. When evaluating a hypoglycemic infant, the first thing to assess is:
   a. Ballard exam.
   b. Presence or absence of symptoms.
   c. Airway, breathing, circulation.
   d. Presence or absence of a suck reflex.

4. What is the formula to calculate the glucose infusion rate and at what level should you start?

5. Which of the following infants are at risk for hypoglycemia and should have a screening blood sugar performed in the term nursery? (more than one answer)
   a. Infant of diabetic mother.
   b. A jittery infant.
   c. Small for gestational age infant status post difficult delivery.
   d. 37 week infant born to a GBS positive mother.

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Answers to questions

1. False
2. a
3. c
4. GIR = (dextrose % x ml/kg/d) / 144. Start at 6-8 mg/kg/min and titrate.
5. a, b and c are all correct.

Chapter III.9. Neonatal Seizures
Lynn M. Iwamoto, MD

This is a term female infant born to a 28 year old mother who is A+, serologies unremarkable, and group B strep (GBS) negative with no preexisting medical problems. Labor and delivery was notable for a tight nuchal cord. The infant was delivered vaginally. Brief oxygen blow by and tactile stimulation were required. Apgar scores were 7 (-1 tone, -2 color) and 9 (-1 color) at 1 and 5 minutes, respectively. Initial glucose screen was 40mg%. The infant had no respiratory distress and fed adequately overnight. Early in the morning on the second day of life, she has a 1 minute generalized tonic-clonic seizure. She is taken to the nursery and oxygen is administered. The rapid glucose is 60mg%. An IV is started and a loading dose of phenobarbital is given. She is then transferred to the NICU. She then has a second seizure, initially noted to start in the right arm which then becomes generalized. In retrospect, slight decreased fetal movements were noted, in utero.

Exam: VS T36.8, P140, R60, BP 90/50, birth weight 3300g. Length and head circumference are at the 50th percentile. She is in no respiratory distress, but she is sleepy. Head shows mild molding, no caput or cephalohematoma. No dysmorphic features are evident. Lungs are clear to auscultation. Heart regular without murmurs. Abdomen with normal umbilicus, no masses, no hepatosplenomegaly and normoactive BS. Normal female genitalia. Extremities are well perfused with good pulses. There is mildly decreased generalized tone. DTRs are 2+ and symmetric.

The infant requires a second dose of phenobarbital. Maintenance dosing is started. No further seizures are noted. Electrolytes and glucose are normal except for a bicarbonate level of 19. BUN, Cr, Ca, P, and Mg are normal. CBC is remarkable for a hemoglobin of 12 g/dl, hematocrit 36% (anemic for a newborn), normal WBC and differential, normal platelet count. A lumbar puncture is performed which shows normal CSF findings. An MRI scan shows an increased signal in the left hippocampus, suggesting ischemic injury. EEG shows moderate burst suppression.

Most neonatal seizures occur within the first few days of life, with an incidence between 1.8 and 3.5 per 1000 live births (1). The clinical manifestations of seizures in newborns differ significantly from that seen in older children and adults as the human neonatal brain is still in the process of organization and development. Premature infants have a higher frequency of seizures and their seizures are less organized (2).

Seizures in newborns can be classified as subtle, clonic, tonic, or myoclonic (3). Subtle seizures are often difficult to recognize, they occur more frequently in premature infants, and they are not always correlated with electroencephalographic seizure activity. Examples of subtle seizures include bicycling movements, autonomic dysfunction, horizontal eye deviation, and repetitive facial movements. Clonic seizures are slow, rhythmic movements. They can be focal or multifocal. Tonic seizures can be focal or, more commonly, generalized. They consist of sustained extension and/or flexion posturing. Lastly, myoclonic seizures are composed of rapid, flexion twitching or jerking movements. These seizures can be focal, multifocal, or generalized.

A clinical seizure results from excessive depolarization of neurons in the central nervous system. The pathophysiology of this excessive depolarization is unclear, but is thought to be related to energy production failure, membrane alteration, excess excitatory neurotransmitters, or deficit of inhibitory neurotransmitters (2). Hypoxemia, ischemia and hypoglycemia can result in significantly decreased energy production and increased release of glutamate, the principal excitatory neurotransmitter in the cerebral cortex. Hypocalcemia and hypomagnesemia cause increased depolarization by increasing sodium influx across the neuronal cell membrane. In addition, the inhibitory pathways are not well developed early in life.

Neonatal primary seizure disorders, epileptic syndromes, do occur, but at a very low frequency. The major etiologies of neonatal seizures include hypoxic-ischemic encephalopathy, intracranial hemorrhage, metabolic disturbances, intracranial infection, developmental defects, and drug withdrawal.

The most common cause of neonatal seizures is hypoxic-ischemic encephalopathy (HIE) brain injury. Asphyxial injury may occur in utero as a result of decreased uteroplacental perfusion, for example in abruptio placenta, cord compression, preeclampsia, or chorioamnionitis. Postnatally, conditions such as persistent pulmonary hypertension of the newborn, cyanotic congenital heart disease, sepsis, and meningitis can also result in hypoxic-ischemic brain injury. In those infants with HIE who have seizures, onset of seizures is generally within the first 24 hours after birth. However, the timing of onset is not a reliable indicator of the timing of the neurologic injury (4).

Seizures due to intracranial hemorrhage may also be associated with hypoxic-ischemic or traumatic injury since these events are frequently associated with each other. Onset of seizures due to subarachnoid hemorrhage or subdural hemorrhage is usually the second or third day of life, while those due to germinal matrix-intraventricular hemorrhage present after the third day (2).

CNS infections can also be associated with neonatal seizures. Congenital infections with viruses (cytomegalovirus, rubella, herpes, and others) or toxoplasmosis can cause severe encephalopathic disease. Seizures also often occur in neonates with acute intracranial bacterial infections, most commonly Escherichia coli and group B streptococcal meningitis.

Metabolic disturbances such as hypoglycemia, hypocalcemia, and hypomagnesemia are associated with neonatal seizures. Newborn infants who are premature and infants of diabetic mothers (large for gestational age, or small for gestational age) are most at risk for hypoglycemia. Those infants who are of low birth weight, born to diabetic mothers, or who have suffered hypoxic-ischemic injury are also at risk for hypocalcemia. Hypomagnesemia often accompanies hypocalcemia. Other metabolic abnormalities associated with seizures include local anesthetic intoxication, hyponatremia, and inborn errors of metabolism (2,5).

Diagnostic evaluation includes glucose, electrolytes, calcium, magnesium, and phosphorus in order to identify an immediately correctable metabolic condition. Spinal fluid analysis is performed to identify a potential bacterial infection. CT and magnetic resonance imaging (MRI) can delineate the brain anatomy with high sensitivity and resolution (MRI better than CT). Lesions of hypoxic-ischemic injury can be identified within the first 2-3 days after the asphyxial event (6). The electroencephalogram (EEG) is used to confirm the presence of seizure activity and to define the background electrical activity which is valuable in estimating prognosis.

Treatment of neonatal seizures should focus on the primary etiology as well as direct seizure control. Neonates are less likely to incur seizure related injury. Phenobarbital is often used as the first line anticonvulsant, followed by phenytoin and lorazepam. Oral phenytoin is poorly absorbed from the infant GI tract.

Prognosis varies as a function of primary etiology and gestational age of the infant. The background EEG activity is also correlated with outcome in both term and preterm infants. Infants with a normal background activity are less likely to have neurological sequelae as

opposed to those with moderate to severe abnormalities such as burst-suppression pattern, voltage suppression, and electrocerebral silence (2).

Questions

1. True/False: Neonatal seizures are always the tonic-clonic type.

2. Which of the following conditions is LEAST likely to be associated with neonatal seizures?
   a. E. coli meningitis
   b. syndrome of inappropriate diuretic hormone
   c. transient tachypnea of the newborn
   d. umbilical cord prolapse

3. True/False: Oral phenytoin is often used as a first line anticonvulsant. Why or why not?

4. Facial twitches are an example of what kind of seizures?
   a. tonic-clonic
   b. myoclonic
   c. clonic
   d. subtle

5. True/False: Neonates have an immature inhibitory neurotransmitter system.

6. Which of the following would be LEAST helpful in the immediate diagnostic evaluation of an infant with a neonatal seizure?
   a. brain ultrasound
   b. serum glucose level
   c. cerebral spinal fluid gram stain
   d. serum calcium level

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Answers to questions

1. false
2. c
3. false, since it is poorly absorbed from the infant GI tract.
4. d
5. true
6. a

Chapter III.10. Neonatal Sepsis
Sherry W.H. Loo, MD

This is a 3200 g term newborn female delivered via normal spontaneous vaginal delivery to a 25 year old G1P0 syphilis non-reactive, group B strep (GBS) negative, rubella immune, hepatitis B surface antigen negative mother with early preeclampsia and thrombocytopenia (platelet count 80,000). Rupture of membranes occurred 11 hours prior to delivery with clear fluid. Intrapartum medications included 3 doses of butorphanol (narcotic opioid analgesic). The last dose was administered within 1 hr of delivery. There was no maternal fever. Apgars were 8 and 9.

In the newborn nursery, vital signs are: HR 140, T 37, BP 47/39, RR 54. Oxygen saturation is 98-100% in room air. The infant appears slightly pale and mottled. She is centrally pink with persistent grunting, shallow respirations, and lethargy. Her fontanelle is soft and flat. Heart exam is normal. Lungs show good aeration. Abdomen is soft and without masses. Pulses are 1+ throughout with 3-4 sec capillary refill. Neuro exam shows decreased tone and a weak, intermittent cry.

Labs: CBC with WBC 3,200, 6% segs, 14% bands, 76% lymphocytes, Hgb 15, Hct 43, platelets 168,000. Blood glucose 52. The chest x-ray is rotated with fluid in the right fissure, diffuse streakiness on the left, and a normal cardiac silhouette. CBG (capillary blood gas) pH 7.31, pCO2 43, pO2 44, BE-4. CSF: 2430 RBCs, 20 WBCs, 1% PMN, 17% lymphs, 82% monos, glucose 39, protein 133, gram stain shows no organisms.

You are asked to consult on this case. What other tests would you obtain? What would your assessment be for this infant? What would your recommendations be (if any) for further evaluation or treatment? If you were to treat this infant, how long would you treat her?

The evaluation and management of the neonate at risk for sepsis is potentially a source of frustration for students and practitioners. The convention in the past has often been to evaluate and empirically treat all neonates felt to be at significant risk, especially as relates to maternal factors and the receipt of maternal antibiotics in labor. Due to evolutions in health care and the advent of intrapartum prophylaxis for group B streptococcal sepsis (mothers are routinely screened for group B strep and if found to be positive, they are given ampicillin prior to delivery), more attention has come to focus (very appropriately) on the clinical evaluation of the infant as a major part of the decision to evaluate and treat with antibiotics. This factor; however, remains fraught with a degree of uncertainty related to the nonspecific manifestations of infection in the newborn, the sometimes rapid progression of sepsis in the newborn, and the lack of laboratory tools which have high positive predictive accuracy.

The approach in this section of neonatal sepsis will be to: 1) incorporate the evolutionary changes in management which are based on more recent evidence; 2) to emphasize the lack of a gold standard underlying the variations in practice (i.e., clinical sepsis with a negative blood culture is still more often diagnosed than blood culture proven sepsis); and 3) to suggest (based on interpretation of older and recent evidence) newer concepts which place more reliance on tests with high negative predictive accuracy and the efficacy of intrapartum antibiotics (1-7).

The information upon which former standard practice is based is also provided throughout the chapter. These are necessary and basic to understanding the problem of neonatal sepsis and perinatal infections. However, the evaluation and management will de-emphasize empiric treatment for risk alone, and variation in practice will be seen as a necessary consequence of our lack of knowledge and the inherent variation in individual practitioner's tolerance of degree of risk and uncertainty.

Table 1. Common bacterial and viral infectious agents causing sepsis (or something similar to sepsis):
- E. Coli
- Group B streptococcus (GBS)
- Listeria monocytogenes
- Herpes simplex
- Cytomegalovirus
- Any virus infecting the mother in the week prior to delivery any bacteria cultured from the mother on admission for labor

Table 2. High risk factors for neonatal sepsis:
- Late maternal prenatal care
- Maternal UTI, STD, or abnormal serologies
- Prolonged rupture of membranes (>24 hrs)
- Maternal fever prior to delivery
- Maternal chorioamnionitis
- Prematurity
- GBS positive screen without intrapartum prophylaxis

Table 3. Signs and symptoms of neonatal infection (most are NONSPECIFIC):
- Apnea and dusky episodes for no clear reason.
- Lethargy, poor color, hypoactivity, poor capillary refill.
- Feeding intolerance (more than usual spit-up), abdominal distention.
- Clinical appearance; doesn't look "good".
- Tachypnea, temperature instability, look of distress.

Table 4. The most important risk factors for neonatal sepsis:
- Prematurity
- Untreated maternal chorioamnionitis.
- Untreated maternal prolonged rupture of membranes.
- Maternal fever, untreated.
- Untreated positive maternal GBS screen.

Table 5. Equivocal risk factors (i.e., they overlap or may result in similar manifestations):

Fetal distress.
Depression at birth (needs resuscitation, low 5 minute Apgar).
Meconium staining.
Hypoglycemia.
Any unusual finding which may be due to infection.

Although we have gained more knowledge about risk factors and have more antibiotics at our disposal, there is still NO GOLD STANDARD for the diagnosis of neonatal infection. There are still many unknowns in neonatal sepsis which continue to elude us, and compel the diagnosis of neonatal infection to be made clinically more often than not.

Table 6. The Unknowns in Neonatal Sepsis:

1. How effective is GBS prophylaxis as prescribed? >95%
2. How sensitive are blood cultures (i.e., how often are they positive) ?
3. Can an elevated I/T ratio (immature to total granulocyte ratio) indicate acute OR resolving inflammatory response?
4. Will ampicillin resistant organisms be seen with more use of intrapartum ampicillin prophylaxis?
5. What is the minimum duration of antibiotic treatment to effectively treat sepsis?
6. Is neonatal infection with a positive blood culture the same as neonatal sepsis?
7. When does neonatal sepsis become SIRS (systemic inflammatory response syndrome), i.e., overwhelming sepsis?
8. What is the immunologic competence level of a given infant at risk (i.e., will the infant be able to respond positively with appropriate antibiotics)?
9. Does intrapartum treatment of the mother for chorioamnionitis also treat the fetus effectively?

Because we have many unknowns and the worst case scenario for neonatal infection is sepsis and perhaps overwhelming sepsis or death from SIRS, pediatricians have tended to err on being conservative in the evaluation for sepsis. This intention paradoxically results in a more "aggressive" approach to the patient in terms of tests and/or treatment. This paradox is underscored by the lack of a gold standard for diagnosing sepsis in the newborn, and complicated by the recent increase of intrapartum antibiotics prescribed to women in labor.

Table 7. The full sepsis work-up.

1. CBC differential, platelet count.
2. Blood, urine, and CSF cultures.
3. CXR. Add a tracheal aspirate for gram stain and culture if the patient is intubated.
4. Equivocal: gastric aspirate for gram stain and culture.
5. Start broad spectrum antibiotics while awaiting culture results.

For a partial sepsis work-up, one could pick any one or more of the above items. For a totally asymptomatic infant with high risk factors, none of the steps might be elected (practice variation). This is based on the premise that the clinical appearance and serial monitoring of the infant is just as accurate as any laboratory test for indicating the presence of infection, given any set of risk factors in an infant with a relatively normal exam.

This wide variation of practice suggests that the unknowns in neonatal sepsis (see above) are quite important to practical management. This may lead one to be more or less restrictive in practice, and requires one to have thorough knowledge of the predictive accuracy of the objective tools available in the assessment of neonatal sepsis. From an outcomes point of view, one would expect that if certain practices were inappropriate, there would be a higher rate of readmission within two weeks of discharge from the normal nursery for those regimens which were "least restrictive." Such evidence has not emerged from this institution, based on a review of early discharge from the nursery in the mid-1990's, when the most common cause for readmission was jaundice (infection and sepsis were not found).

The highest degree of controversy surrounds the group of infants who are asymptomatic with some risk factors for sepsis, especially those whose mothers received intrapartum antibiotics. In these infants, there is the fear of partially treated sepsis, prompting evaluation and treatment of these infants based on their risk factors and discounting the maternal antibiotics. However, the asymptomatic state could also be interpreted as adequate prophylactic treatment for neonatal bacteremia. In 1990, Wiswell et al., reported on a survey of academic infectious disease departments with respect to management of this scenario. They concluded that there is no consensus regarding management of pretreated, healthy appearing, term gestation neonates (8). In contrast, Teji et al (1994) surveyed neonatologists in Midwestern states of the U.S. with regard to the management of PROM (prolonged rupture of membranes) without chorioamnionitis, chorioamnionitis without treatment prior to delivery, and chorioamnionitis with treatment prior to delivery. One hundred thirty seven responses were received and prematurity and severity of maternal illness significantly influenced the decision to treat empirically, irrespective of screening test results (9). More recently, Eichenwald (1997) has suggested a very reasonable scheme for evaluation of the asymptomatic term infant, based on a protocol developed by the Joint Program in Neonatology in Boston (Table 8) (10). However, the question persists and evolves regarding the benefits and risks of routine therapy of high risk neonates vs. clinical observation and selective therapy of only those infants who manifest symptoms. This evolution is highlighted by the recent reports of ampicillin-resistant organisms in neonatal sepsis (11-13) and the dramatically increased incidence of Candida species sepsis in very premature infants in NICU settings over the last decade, of which one very important contributor is the prior use of antibiotics.

Table 8. Management of asymptomatic term infants with risk factors for infection for term, well appearing infants with maternal antibiotics given in labor.

Tests: CBC, differential, platelet count, blood culture (volume of blood is important; 1cc recommended).
Antibiotics until 48 hour blood culture results are available if:

1. I/T>0.2 (immature neutrophils to total neutrophil ratio) or
2. WBC <5000 or
3. Mother received antibiotics for suspected or diagnosed chorioamnionitis.
4. GBS positive mother, adequately treated, but with a history of a previously affected infant with invasive GBS infection

In this scenario, the availability of rapidly available tests with high negative predictive accuracy would seem particularly useful. Several fitting this category are:

1. The total WBC and l/T ratio (14)
2. Serial CBC's using total WBC and l/T ratio (15)
3. A hematologic scoring system (16)
4. A combination of CRP and IL-6 (17)

Singhal and La Gamma (1996) in a study of 6620 pregnancies, found that 82% of at-risk patients are asymptomatic and have negative body fluid cultures. They concluded that their data support restricting a full course of antibiotic treatment to only those patients with clinical or laboratory signs of sepsis (18%) (5). Escobar et al (2000) reported on a large population of newborns in the Kaiser system of whom 15% were evaluated for sepsis (4). Only 2.2% met criteria for proven, probable, or possible bacterial infection, and of those meeting criteria, 0.8% had positive cultures while 1.4% had clinical evidence of bacterial infection. 1568 out of 2785 infants evaluated were not treated, and the initial asymptomatic status was associated with a decreased risk of infection (adjusted odds ratio; AOR=0.26). Factors associated with increased AOR for infection were chorioamnionitis, low absolute neutrophil count, and meconium stained amniotic fluid. They concluded that evidence based observation and treatment protocols could be defined, based on a limited set of predictors: maternal fever, chorioamnionitis, initial neonatal examination, and absolute neutrophil count (4). Ultimately, each practitioner must determine the degree of risk or uncertainty that he or she can accept on the basis of clinical and institutional experience.

Table 9. A revised and composite screen and evaluation for sepsis in the neonate.

Risk factors: Prematurity, chorioamnionitis, prolonged rupture of membranes, maternal fever, fetal tachycardia and depression at birth.

Screening tests: CBC and differential and platelet count; total WBC and I/T ratio (initial and serial); blood culture; urine culture or GBS antigen; others as may be available to increase negative predictive accuracy such as CRP, IL-6; clinical exam of the infant.

Completing the evaluation: Lumbar puncture for CSF studies and culture; CXR and/or endotracheal aspirate for gram stain and culture.

Treatment: Institute broad spectrum antibiotic coverage for neonatal sepsis. If meningitis is suspected, add cefotaxime to the regimen.

For premature infants in whom the physical exam may be more equivocal and whose prematurity constitutes an additional risk factor, the threshold for a full sepsis evaluation and antibiotic treatment is much lower.

Table 10. Rates of infection in neonates and mortality rates.

Proven sepsis: 2.5 per 1000 live births, mortality 8.7% (18).
Clinical sepsis: 3.6 per 1000 live births, mortality 4.3% (18).
VLBW (very low birth weight) proven sepsis: 26.5 per 1000 live births (18).
VLBW clinical sepsis: 32.4 per 1000 live births (18).
EOGBS (early onset GBS) 0.5 per 1000 live births, mortality 10% (19).
Other early onset infection 0.5 per 1000 live births (19).

Questions

1. For the case presented at the beginning of this chapter, you are asked to consult on this case. What other tests would you obtain'?
2. What would your clinical assessment of this infant be?
3. What would your recommendations for further evaluation and/or treatment be?
4. If you were to treat this infant, how long would you treat?
5. What tests have the highest positive predictive accuracy in neonatal sepsis?
6. What tests have the highest negative predictive accuracy in neonatal sepsis?
7. Is the volume of blood obtained for the blood culture important to the culture being positive or negative?
8. Is there good evidence that treatment of maternal chorioamnionitis prior to delivery significantly reduces the risk of neonatal infection?
9. Does prophylaxis for group B strep infection alter the time course of early onset group B streptococcal sepsis if prophylaxis is ineffective?
10. What is the incidence of neonatal sepsis and what is the mortality from neonatal sepsis?

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Answers to questions

1. Blood and urine cultures, if not already done.

2. Clinical sepsis with poor perfusion and neutropenia; possible septic shock with narrow pulse pressure.

3. a) Repeat CBC to monitor the neutropenia and thrombocytopenia. b) Volume bolus to improve perfusion. c) Follow-up exam of abnormal tone and cry after instituting supportive therapy. d) Start broad spectrum antibiotics parenterally. e) Transfer from the normal nursery to a higher level nursery or intensive are unit for continuous monitoring of vital signs.

4. Seven to ten days empirically, given the clinical presentation and depending on culture results. Serial CRPs may also be used to assist with duration of treatment.

5. Any 2 from the battery reviewed by Sinclair (14) gave 62% for sepsis proved or probable.

6. Again any 2 from the above reference (14) gives 98% negative predictive accuracy for sepsis proved or probable. However, the CBC and differential alone will give you two out of this battery.

7. Yes. At least one ml should be obtained for blood cultures.

8. Yes

9. No. This has implications for the current AAP protocol for monitoring infants whose mothers did not receive prophylaxis.

10. 2.5 per 1000 live births, with mortality rate of 8.7% (18). Clinical sepsis is cited as 3.6 per 1000 live births with mortality of 4.3%. Figures are much higher for VLBW infants.

Chapter III.11. Congenital and Perinatal Infections
Sheree Kuo, MD

Case 1

You are asked to attend the precipitous vaginal delivery of an estimated 33 week gestation infant whose estimated fetal weight is 1800 grams. Mother is a 26 year old gravida 5, para 4 woman who was admitted in active labor 45 minutes ago. She did not seek prenatal care with this pregnancy, but reports no medical problems during the pregnancy. She denies tobacco, alcohol and illicit drug use. Mother's blood type is O+, antibody negative. All other prenatal labs are pending. Prior to delivery, mother received one dose of ampicillin only. Membranes are ruptured at the time of delivery revealing clear amniotic fluid.

At delivery, you receive a small, but vigorous male infant and bring him to the warming table. He is quickly positioned, dried, and stimulated. He is pink with good respiratory effort and his heart rate is 150 beats per minute. You note his skin is mildly jaundiced with raised red/purple lesions. You allow the mother to bond briefly with the infant and inform her that because you suspect the infant has a congenitally acquired infection, you are transferring him to the special care nursery for a more detailed examination and further management.

Exam: VS T 37.5, P120, RR 40, BP 60/36, oxygen saturation 100% in room air. Ballard exam: 38-40 weeks gestation. Growth parameters: weight 1.845 kg (<5%ile for 38 weeks, 50%ile for 33 weeks), length 44cm (<5%ile for 38 weeks, 50%ile for 33 weeks) and head circumference 31.5 cm (5%ile for 38 weeks, 50%ile for 34 weeks). He is a small, thin male infant with little subcutaneous fat, who is in no acute distress. His skin is mildly jaundiced with the "blueberry muffin" appearance of diffuse raised red/purple lesions and petechiae. His anterior fontanelle is soft, but full. His sclerae are mildly icteric. The abdomen appears distended and protuberant, but it is soft and non-tender. A firm liver edge is felt 4 cm below the right costal margin and the spleen is felt 3 cm below the left costal margin. The remainder of the examination is unremarkable.

On admission, you order a CBC with differential, liver function tests, fractionated bilirubin levels and a urine culture for CMV. The CBC is remarkable for moderate anemia (Hct = 30%), thrombocytopenia (50,000) and atypical lymphocytosis (10%). Both SGOT (210 mU/mL) and direct serum bilirubin (8 mg/100mL) are elevated. Three hours after birth, the infant develops generalized tonic-clonic seizures that stop after administration of 20mg/kg of phenobarbital. Cranial ultrasound done the next morning reveals periventricular calcifications and generalized brain atrophy. These findings are most consistent with congenital cytomegalovirus infection. To complete the workup you consult ophthalmology to evaluate the patient for chorioretinitis.

Case 2

A former 31-week premature male infant is now four weeks old and nearly ready for discharge from the intermediate nursery. At birth, he was delivered at an outlying hospital via emergent caesarean section for placental abruption to a 25 year-old G1 female with negative serologies and an otherwise unremarkable prenatal course. At the time of delivery, he required resuscitation and was transfused with O negative blood in the delivery room for a hematocrit of 15%. After stabilization, he was transferred to your facility where he has done well for the past month. Today, he has had a sudden deterioration in his respiratory status accompanied by hypotension.

Exam: VS T 36.0 rectal, P 178, RR 90, BP 40/23, oxygen saturation 84% on RA. Growth parameters are all at the 50% for 35 weeks' gestation. He is a pale, mottled premature male infant in moderate to severe respiratory distress. His skin is mildly jaundiced. His mucous membranes are pale. He has nasal flaring with intercostal and subcostal retractions. He is tachypneic with coarse breath sounds. His heart has an increased rate, but regular rhythm. His pulses are barely palpable in his extremities and his capillary refill is 4-5 seconds. His abdomen is soft, but no bowel sounds are present. The remainder of the examination is unremarkable.

Suspecting nosocomial bacterial infection, you perform a CBC, blood culture, urinalysis, and spinal tap. Antibiotics for nosocomial infection are started. Initial urine and CSF studies are normal. CBC is remarkable for an elevated white count with lymphocytosis. The baby has moderate anemia (Hct = 32%) and thrombocytopenia (platelets = 30,000). Chest x-ray shows new diffuse symmetric infiltrates bilaterally. Tracheal aspirate shows moderate WBCs but no organisms on gram stain. After 48 hours on antibiotics, there has been no improvement in his clinical condition. The infant remains intubated on high ventilator settings and dopamine for persistent hypotension. His blood, urine, tracheal aspirate and CSF cultures are all negative for growth. You wonder about CMV infection in light of his pneumonia, shock and history of blood transfusion at the time of delivery and send his urine for CMV culture. Two days later, his urine culture is found to be positive.

Case 3

A young mother rushes into the emergency department with a baby swaddled in her arms. She reports that earlier today, her one week old son developed a low grade fever that she attributed to overbundling. However, throughout the course of the day, his interest in feedings has diminished and he is now difficult to arouse. There is no history of vomiting, breathing difficulties, URI symptoms, diarrhea, or change in bowel and bladder pattern. She denies excessive weight loss as the infant was seen by his primary care physician yesterday.

His birth history is noncontributory: he was born at 39+ weeks gestation via normal spontaneous vaginal delivery to a 23 year-old G1 female who had good prenatal care. Prenatal labs are unremarkable. Mother denies any history of sexually transmitted diseases or abnormal Pap smears. There was no history of prolonged rupture of membranes or maternal fever. Apgar scores were 9 and 9 at 1 and 5 minutes. Birthweight was 3750 gms (75%ile). The infant had an unremarkable hospital course and was discharged home on day 2 with mother.

Today's exam: VS T 39.0, HR 160, RR 40, BP 75/52, oxygen saturation 95% in room air. Growth parameters: weight 3.695 kg (75%ile), length 50 cm (50%ile) and head circumference 35.5 cm (>50%ile). He is a well developed, well nourished term male infant who appears sleepy and lethargic. When he does awake, he is difficult to console and displays a weak, high pitched cry. He is pale, but in no acute distress. He has mild facial jaundice, but no other skin lesions. His anterior fontanelle is soft, but full. Mucous membranes are moist. The abdomen is soft and non-tender. The liver edge is felt 2 cm below the right costal margin and the spleen tip is palpated just below the left costal margin. Neurologically, the infant has decreased tone throughout his extremities and he is difficult to arouse.

You order a complete sepsis workup consisting of a CBC with differential, blood culture, urinalysis, urine culture, and cerebral spinal fluid for glucose, protein, cell count with differential, gram stain, and culture. You obtain an extra tube of CSF to be held in the lab. IV access is obtained and the infant is immediately given ampicillin and gentamicin. IV fluids are also started in light of his decreased level of consciousness and poor appetite. Prior to transfer to the pediatric wards, the patient develops rhythmic right-sided tonic-clonic movements. After administering IV phenobarbital, the seizures stop. You then order IV acyclovir and call the lab to run PCR for herpes

simplex virus and enterovirus on the extra tube of CSF. This clinical presentation is consistent with a perinatal infection, possibly due to herpes simplex virus.

Infections in the newborn infant can be classified as congenital or perinatal. It is important to make this distinction as the clinical presentations, causative organisms, diagnostic approaches, treatments and long-term considerations differ for these two groups. A congenital infection is an infection seen in the newborn infant that was acquired transplacentally during the first, second, or early third trimester. In contrast, a perinatal infection is acquired either around the time of delivery or during the first week of extrauterine life.

The incidence of congenital infection in the fetus and newborn infant is relatively high at 0.5-2.5%. The most common causative agents are rubella virus, cytomegalovirus (CMV), Toxoplasma gondii, Treponema pallidum, human immunodeficiency virus (HIV), human parvovirus B19 and Epstein-Barr virus (EBV). Despite the diversity of these organisms, many produce similar syndromes in the newborn infant. Common manifestations of congenital infections include growth retardation, hepatomegaly, splenomegaly, jaundice (secondary to direct hyperbilirubinemia), hemolytic anemia, petechiae and ecchymoses, microcephaly, hydrocephaly, and pneumonitis. However, the majority of affected infants are entirely asymptomatic.

The incidence of congenital rubella syndrome is 0.5 per 1000 live births. Infants are usually born small for gestational age. Common clinical findings include: purpura, thrombocytopenia, hepatosplenomegaly, cardiac defects, eye defects (glaucoma and cataracts), pneumonia and meningoencephalitis. Diffuse purpuric lesions on the skin resembling a "blueberry muffin", represent cutaneous extramedullary hematopoietic tissue that may be seen in this and other congenital infections. Congenital rubella infection can be diagnosed with an elevated anti-rubella IgM titer in the perinatal period or high anti-rubella IgG titers throughout the first year of life. Virus can also be isolated from a throat swab, CSF or urine. Common long term problems seen in infants with congenital rubella include communication disorders, hearing defects, mental and/or motor retardation, microcephaly, learning deficits, balance and gait disturbances, and behavioral problems. Although live attenuated rubella virus vaccine is available to prevent the disease, there is no specific therapy for congenital rubella.

Annually, approximately 40,000 infants are born with congenital CMV infection in this country. Twelve percent of these infants will die and more than 90% of survivors will suffer late complications, most commonly sensorineural hearing loss. Congenital CMV infection may be the result of a newly acquired maternal infection or a reactivated old maternal infection. Although less common, newly acquired maternal infection poses a much higher risk of severe disease and a worse prognosis. Ninety percent of infected newborns are surprisingly asymptomatic at birth. However, those that are symptomatic are small for gestational age and often present with petechiae, ecchymoses, thrombocytopenia, jaundice, direct hyperbilirubinemia, anemia, hepatosplenomegaly, elevated SGOT, microcephaly, seizures and chorioretinitis. The diagnosis of congenital CMV infection is best made by isolating the virus in urine culture. Periventricular calcifications can be seen on cranial ultrasound. Of the affected infants that survive the neonatal period, 1/3 will have hearing loss, one third will have neuromuscular disorders (seizures or spasticity) and a few will have vision problems secondary to chorioretinitis. Although there is no specific therapy for congenital CMV infection, trials examining the effectiveness of ganciclovir, alpha interferon and CMV immune globulin are underway (1).

The incidence of congenital toxoplasmosis infection varies with geographic location and local dietary habits. Maternal toxoplasma infection is usually due to ingestion of tissue cysts found in raw or undercooked meats or consumption of water or other foods containing oocysts from infected cats. Congenital infection with Toxoplasmosis gondii occurs during maternal parasitemia. In the neonate, the primary focus of toxoplasma infection is in the central nervous system, leaving necrotic, calcified cystic lesions dispersed within the brain. Less commonly, similar lesions can be found in liver, lungs, myocardium, skeletal muscle, spleen and other tissue. Approximately 85% of infants with congenital infection have normal examinations and are asymptomatic. Those infants that exhibit illness at birth frequently present with fever, hepatosplenomegaly, jaundice, rash and pneumonitis. The classic triad of toxoplasmosis, chorioretinitis, hydrocephalus and intracranial calcification occurs in only a small proportion of symptomatic patients. Abnormal laboratory findings include anemia, thrombocytopenia, eosinophilia, and abnormal CSF studies. Seizures, mental retardation, spasticity, and relapsing chorioretinitis are common long-term complications of congenital toxoplasmosis, even if not present at birth. Prenatal diagnosis is made between 20 and 26 weeks by detection of IgM anti-Toxoplasma antibodies and on isolation of the parasite from fetal blood or amniotic fluid. Antenatal ultrasound can suggest the diagnosis of congenital toxoplasma infection when bilateral, symmetric ventricular dilatation, intracranial calcifications, increased placental thickness, hepatomegaly and ascites are noted. Postnatal diagnosis is also made by detection of anti-Toxoplasma IgM antibodies in the infant's serum. Treatment, antenatally and postnatally, consists of pyrimethamine and sulfadiazine. Spiramycin may also be used, if available. Historically, prognosis in untreated infants is poor. However, with recent advances in antenatal diagnostic capabilities and available medical therapies, the frequency of major neurologic sequelae has decreased (2).

Syphilis is caused by the spirochete Treponema pallidum. Transplacental transmission usually occurs during the second half of pregnancy. Most infants born to mothers with primary or secondary syphilis have congenital infection; though only half of those who are infected are symptomatic. Because congenital syphilis is associated with significant neurodevelopmental morbidity, it is imperative that both maternal status and infant risk for syphilis be checked in all pregnancies. Early features of congenital syphilis include hepatosplenomegaly, skin rash, anemia, jaundice, metaphyseal dystrophy, periostitis and CSF abnormalities including elevated protein and mononuclear pleocytosis. However, in some cases, the infant is asymptomatic and may not develop any signs or symptoms of congenital infection for weeks or months. "Snuffles" is obstruction of the nose with initial clear discharge progressing to purulent or sanguineous discharge. It is seen in infants with congenital syphilis usually after the newborn period. Detection of IgM-FTA-ABS (fluorescent treponemal antibody absorption) in the newborn's blood is the most reliable method of diagnosing congenital syphilis. However, this test is not always positive early on in life, thus repeat testing at 3 to 4 week intervals is frequently indicated. Treatment for both the pregnant mother and baby is penicillin G. Despite antibiotic therapy, it is recommended that infants undergo repeat blood and CSF testing during the first 12-15 months of life until negative or stable low titer levels are achieved. Vision, hearing and developmental evaluations are also indicated before three years of age in infants with congenital syphilis (3).

One to two-thirds of adults in the United States are seropositive for human parvovirus B19. However, the overall risk of fetal infection from human parvovirus B19 is low. Fetal infection with the virus can result in neonatal nonimmune hydrops fetalis and fetal aplastic crisis (i.e., severe anemia resulting in high output congestive heart failure and hydrops), but has not been shown to cause congenital anomalies. B19 is known to have an affinity for progenitor erythroid cells in the bone marrow. This affinity most likely produces bone marrow aplasia that may lead to congestive heart failure and nonimmune hydrops fetalis. The diagnosis of B19 infection can be made either serologically (anti-human parvovirus B19 IgG and IgM levels) or by viral culture. Antenatal treatment of infected infants with hydrops includes fetal transfusion and maternal digitalization. No specific antiviral treatment is currently available.

Perinatally acquired infections are those that are acquired either around the time of delivery or during the first week of extrauterine life. Common pathogens include bacteria, such as group B streptococci, E. Coli, and Listeria (covered elsewhere in this text), herpes simplex virus, hepatitis viruses and human immunodeficiency virus. Infants with perinatally acquired viral infections are often normal at birth, developing illness later in life (1).

A few pathogens like cytomegalovirus (CMV) can cause both congenital and perinatally acquired infection in the newborn with striking contrasts in presentation. The infant in Case 1 presents with growth restriction, anemia, thrombocytopenia, extramedullary hematopoiesis, and intracranial calcifications, all indicative of a chronic process; namely, congenital CMV infection that was transmitted transplacentally during the first or second trimester of pregnancy. In contrast, the infant in Case 2 acquired CMV infection after birth resulting in illness several weeks later. Perinatally, CMV can be transmitted through breast milk or vaginal secretions. Premature infants however, are particularly susceptible to transmission through transfusion of blood products. The resulting syndrome is characterized by shock, pneumonitis and lymphocytosis as described above (4). The role of ganciclovir in perinatally acquired CMV infection is unclear.

The majority of neonatal herpes simplex virus (HSV) infection is acquired from the maternal genital tract with an incidence of approximately 1 case per 3500 live births. However, infection may also be acquired after birth from mother or other persons with non-genital tract lesions (e.g., oral herpes, herpetic whitlow) following close contact with the infant or handling. Primary maternal infection is associated with a 50% risk of perinatal/neonatal infection, while a risk of <5% is seen with recurrent maternal infection. Of note, active HSV lesions are present at the time of delivery in only 1/3 of mothers of affected infants. Several defects in cellular immune function contribute to neonatal susceptibility to HSV. Perinatally acquired HSV infection results in massive coagulation necrosis of the liver, lungs, adrenal glands and brain. Most infants are asymptomatic at birth, developing illness during first 1 to 2 weeks of life. Clinical illness can be characterized as being localized or disseminated. Disseminated illness can be further described as those with and those without central nervous system involvement. Systemic symptoms of disseminated HSV infection usually present towards that end of the first week of life, including poor feeding, lethargy, fever, irritability, and seizures with rapid progression to hypotension, disseminated intravascular coagulation, apnea and shock. Skin vesicles are present in less than half of patients. With antiviral therapy, 15-20% of patients die and 40-55% of survivors suffer long-term neurologic impairment. Localized disease may involve the central nervous system alone, the central nervous system and skin, eyes, and oral mucosa or only the skin, eyes and oral mucosa. Except in cases of isolated viral encephalitis, HSV is readily recovered in culture from scrapings of skin vesicles, blood, cerebrospinal fluid, conjunctivae, respiratory secretions, and urine. Once neonatal HSV infection is suspected, antiviral therapy should be started immediately (1). Parenteral acyclovir is the treatment of choice for herpes neonatorum. Treatment duration varies depending on whether the infection involves the CNS and/or is disseminated (5). Despite antiviral therapy, overall outcome for survivors is poor. More than half of infants who survive disseminated disease will develop microcephaly, spasticity, paralysis, seizures, deafness, or blindness. Those with skin involvement may be subject to recurrent vesicular outbreaks for several years. Of note, HSV can also be transmitted in utero during the first or second trimesters of pregnancy. Those fetuses that are not stillborn or spontaneously aborted demonstrate a syndrome similar to other congenital viral infections like CMV. Treatment is supportive as acyclovir has no proven benefit for these infants (1).

The most important of the hepatitis viruses for the general pediatrician is Hepatitis B. The virus is found primarily in the liver parenchyma, but can be found in circulating blood from a few days to many years. Regardless of maternal acute or chronic infection, the virus rarely crosses the placenta, thus perinatal/neonatal infection is most likely acquired from infected maternal blood encountered during the delivery process. Overall, there is 60-70% chance of transmission during delivery if mother has an acute infection at that time. Mothers may also be carriers which still has a risk of transmission to the newborn. In the U.S., hepatitis B surface antigen (HBsAg) carriage rate is relatively low, about 0.1%. However, rates may be as high as 15% in Taiwan and parts of Africa. At birth, infected infants are asymptomatic. By 2 to 6 months of age, liver enzymes are often elevated and infants are antigen seropositive. Occasionally, infection may present with jaundice, fever, hepatomegaly and anorexia, followed by complete recovery or chronic active disease (1). Approximately 95% of perinatally acquired HBV infection can be prevented by early active and passive immunoprophylaxis of infants born to HBsAg positive mothers. Infants born to HBsAg positive mothers should receive the initial dose of hepatitis B vaccine and hepatitis B immune globulin (HBIG) within 12 hours of birth (given at separate injection sites). Infants born to unscreened mothers should receive their first hepatitis B vaccine within 12 hours of birth while awaiting maternal blood test results. If the mother should be found to be HBsAg positive, HBIG should be given within the first week of life. All infants should complete the hepatitis B immunization series by 6 months of age. Infants born to HBsAg positive mothers should be tested for anti-HBsAg antibodies and HBsAg 1 to 3 months after the third dose of vaccine is given to determine those who may be chronically infected and those who may require additional doses of the vaccine. Breastfeeding by an HBsAg positive mother has not been shown to cause hepatitis B infection in infants (6).

Once seen exclusively in children who had received blood products, pediatric human immunodeficiency virus (HIV) infection is now overwhelmingly the result of perinatal transmission (7). There are three distinct modes of transmission of human immunodeficiency virus (HIV) from mother to fetus. Congenital HIV infection results from the transplacental transmission of virus during early pregnancy. Intrapartum transmission may occur following exposure of the infant to mother's blood or as a result of maternal-fetal transfusion during the delivery. Perinatal infection with HIV can occur either during the birthing process or shortly after birth through breastfeeding (8). Risk factors associated with perinatal HIV transmission include maternal viral load (plasma and genital tract), primary infection of late stage HIV, low CD4 count, STDs/other co-infections, pre-term delivery, increasing duration of rupture of membranes, placental disruption, invasive fetal monitoring (eg. scalp probes), vaginal delivery and lack of AZT prophylaxis (9). The transmission rate from mother to infant is approximately 20-30%. However, recent studies have shown that for select HIV-infected women, zidovudine (AZT) may decrease transmission to 8% of their infants (10). Maternal treatment with AZT in combination with elective cesarean section delivery prior to rupture of membranes and the onset of labor has shown further reduction of the transmission rate to 2% (9). Infants with congenital infection present in a similar fashion to other congenital infections and may also exhibit craniofacial abnormalities. Infants with perinatally acquired infection are usually asymptomatic at birth (8). To maximize the opportunity to prevent perinatal transmission of HIV infection, maternal HIV status should be determined during the first trimester of pregnancy. Anti-retroviral therapy should be started in those found to be HIV positive. During labor and delivery, AZT, 2mg/kg should be administered IV during the first hour, then 1mg/kg per hour until delivery. The infant should then be started on AZT syrup, 8-12 hours after birth, 2mg/kg QID until 6 weeks of age when the infant's HIV status can be determined (9,10). Detection of HIV antibody by ELISA or Western blot in the newborn is complicated by transplacental passage of maternal IgG and should not be performed before 18 months of age. Detection of HIV DNA by PCR is the preferred test for diagnosis of HIV infection in infants. Testing should be performed at birth, then at 1-2 months of age, and a third time between 3 and 6 months of age. Any time an infant tests positive, a second repeat specimen should be obtained immediately to confirm the diagnosis of HIV infection. Viral culture for HIV can also be done; however, issues of cost, regional availability and delay in reporting results make it less useful than HIV DNA by PCR. Umbilical cord blood should not be used for testing. If neither PCR or viral culture are

available, detection of the p24 antigen may be used to assess HIV infection status in infants older than one month, though sensitivity is lower than the other two tests (8,10). The diagnosis of HIV infection in an infant is made with positive results on 2 separate specimens using HIV nucleic acid detection, HIV p24 antigen test, or HIV isolation by culture. An infant with at least 2 negative HIV virology tests from separate specimens, 1 of which was performed at 1 month of age and 1 of which was performed after 4 months of age can be considered "not infected with HIV". Finally, because transmission of HIV through breastmilk has been reported, counseling to discourage breastfeeding should be provided to all mothers who are HIV positive (10).

Questions

1. What physical findings in Case 1 suggest this infant has a congenital infection?
2. How does a congenital infection differ from an infection that is acquired perinatally?
3. What are the most common causes for congenital infection?
4. True/False: A term infant with a normal physical exam and no risk factors for infection may have congenital infection.
5. Periventricular calcifications in the brain are seen with which congenital infection? Diffuse calcifications?
6. True/False: An infant born to a woman with recurrent herpes infection is at higher risk for developing herpes neonatorum than one born to a woman with primary herpes infection at the time of delivery?
7. Administration of what agents can prevent 95% of perinatally acquired hepatitis B infections?
8. True/False: Breastfeeding should be encouraged in all mothers who are HIV positive, but do not have AIDS.

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Answers to questions

1. Small for gestational age, microcephaly, jaundice, pale skin, petechiae, blueberry muffin spots, hepatomegaly, and splenomegaly
2. A congenital infection is an infection seen in the newborn infant that was acquired transplacentally during the first, second, or early third trimester. A perinatal infection is acquired either around the time of delivery or during the 1st week of extrauterine life.
3. Rubella virus, cytomegalovirus (CMV) Toxoplasma gondii, Treponema pallidum, human immunodeficiency virus (HIV), human parvovirus B19 and Epstein-Barr virus (EBV)
4. True
5. Periventricular calcifications are seen in congenital CMV while diffuse calcifications in the brain are seen in congenital toxoplasmosis.
6. False
7. Hepatitis B vaccine and hepatitis B immune globulin.
8. False

Chapter III.12. Necrotizing Enterocolitis
Kelly S. Yamasato

This is a 14 day old infant female born to a 24 year old G1P1 mother at 30 weeks gestation via spontaneous vaginal delivery. Birthweight was 1340 g. Apgar scores were 6 and 7 at 1 and 5 minutes. Her early hospital course was remarkable for respiratory distress syndrome and patent ductus arteriosus. Recent problems include apnea and bradycardia of prematurity and feeding intolerance. Her nutritional needs have been met by advancing enteral feedings of preterm formula supplemented with parenteral hyperalimentation. On the day prior to the onset of symptoms, she was no longer receiving hyperalimentation and she was feeding 30 cc every 3 hours. Today she presents with abdominal distention and bilious vomiting. Her stool color has darkened and her urine output is reduced. She is also having more apnea and bradycardia events.

Exam: VS T 36, HR 180, RR 60, BP 63/40, weight 1425 grams. She is lethargic, slightly toxic, and poorly perfused. Cardiac exam demonstrates tachycardia and no murmurs. Lungs are clear. Her abdomen is tympanitic, distended, and questionably tender, with hypoactive bowel sounds. Stool is guaiac positive.

Abdominal radiographs demonstrate pneumatosis intestinalis. She is made NPO and a nasogastric tube is placed to suction. Following an intravenous bolus of normal saline, her tachycardia resolves and she is placed on maintenance intravenous fluids at 150 cc/kg/day. Empiric antibiotic therapy of ampicillin and gentamicin is started. Serial abdominal radiographs and examinations are regularly performed to monitor her status. She begins to show improvement shortly after the initiation of therapy, and enteral feeding is reintroduced 10 days later. Her feedings are slowly advanced. She is discharged from the hospital at 6 weeks of age. She is evaluated for intestinal stricture later in infancy and none is found.

Necrotizing enterocolitis (NEC) is a fulminant syndrome causing bowel wall necrosis, which can lead to air in the intestinal wall, portal venous system, or peritoneal cavity (1). It occurs in 1-5% of neonatal intensive care unit admissions and is the most common GI emergency in neonates (2,3). NEC may affect the gastrointestinal (GI) tract from the stomach to the rectum, although the distal ileum and proximal colon are the segments most commonly involved (2). The incidence of this disease is 1 to 3 per 1000 live births, with 75-95% of cases occurring in premature infants (4,5). Onset is most common between 3 to 10 days of age, with the age of onset inversely related to gestational age at birth (6). The overall mortality rate in NEC may be as high as 30% (7). NEC in full-term infants is associated with a lower mortality rate than that of premature infants (5).

Prematurity and low birthweight (<1500 grams) are important risk factors for NEC. Although findings vary widely, an estimated 10% of infants with birth weights less than 1500 grams develop NEC (7). Enteral feeding is also a suspected risk factor, as more than 90% of infants who develop NEC have been enterally fed (6). Aggressive enteral feeding rates (greater than 20 cc's/kg per day) and the use of formula rather than breast milk are particularly associated with increased NEC incidence (8). Other suggested risk factors include conditions that increase the risk of infection or hypoxia, such as maternal infections during delivery, exchange transfusion via the umbilical vein, polycythemia, congenital heart disease, perinatal asphyxia, and respiratory distress (1,5).

NEC is a multifactorial disease with an unclear pathophysiology. The pathogenesis of NEC is believed to involve triggers such as bacterial colonization, intestinal ischemia, and formula feeding, that activate proinflammatory mediators (7). These mediators lead to intestinal epithelial cell necrosis and ischemic injury (secondary to vasoconstriction) (8), producing the epithelial disruption and bowel necrosis characteristic of NEC. Some of the mediators suspected to play a role include platelet activating factor, nitric oxide, and interleukin-8 (7). Infants with NEC also show increased cyclooxygenase-2 expression, suggesting involvement of this pathway (3). Rapid enteral feeding (2) and increased intraluminal pressure (1) may also contribute to intestinal damage. Immature GI tracts are especially susceptible to the proinflammatory mediator damage that appears to contribute to NEC. Intestinal defenses against inflammatory injury are not completely developed (7,8). For example, premature infants may have deficiencies in protective compounds such as erythropoietin, epidermal growth factor, and intestinal trefoil factor (7). In addition, premature infants display under-developed immunologic and digestive functions, increasing their risk of intestinal infection. Decreased small intestine motility in premature infants may also contribute to NEC by facilitating bacterial overgrowth and bowel distention (8). Although bacteria such as Pseudomonas, Klebsiella, some E. coli strains, Salmonella, and Clostridium butyricum are suspected to have a role in NEC (1), no pathogen is identified in most cases (2). The role of intestinal hypoxia in NEC has not been established (8), however, congenital heart disease or a patent ductus arteriosus may contribute to the development of NEC by reducing gut perfusion (ischemia) (9).

Early signs and symptoms of NEC involve abdominal distention with gastric retention, episodes of apnea, and vomiting (1,6). Visible blood in the stool occurs in about 25% of patients (2), while occult blood occurs more frequently. NEC often progresses rapidly and may quickly lead to intestinal perforation, shock, and septicemia (1). Pneumatosis intestinalis (gas in the bowel wall) is nearly diagnostic of NEC and is estimated to occur in about 75% of cases. Portal venous gas (PVG), another virtually pathognomonic sign, is seen about 10-30% of the time. The radiographic appearance of PVG is characterized by gas lucencies visible over the liver on x-ray or air bubbles imaged on ultrasound. PVG usually indicates more severe disease (10).

NEC is most commonly staged using the following system proposed by Bell, et al (6,8,11):

Stage 1: Suspected NEC involving a wide range of nonspecific symptoms such as mild abdominal distention, apnea, guaiac-positive stools, lethargy, and bradycardia.

Stage 2: NEC is proven, primarily by the detection of intestinal dilatation and pneumatosis intestinalis through abdominal radiography. Stage 2 NEC mortality rates approximate 15%.

Stage 3: Advanced NEC possibly involving septic shock, respiratory and metabolic acidosis, disseminated intravascular coagulation, neutropenia, and ascites. Pneumoperitoneum may be present. The mortality rate for stage 3 NEC is approximately 60%.

One of the primary diagnostic tools in NEC is the abdominal radiograph. The abdominal radiograph may be used to detect nonspecific early signs of NEC, such as diffuse intestinal gaseous distention or asymmetric bowel gas patterns. However, its major use is to confirm or monitor for the development of NEC by detecting pneumatosis intestinalis. Suspected NEC usually warrants a series of abdominal films every 12 to 24 hours for a minimum of 2 to 3 days to monitor for pneumatosis intestinalis. Contrast enemas are not commonly used in the diagnosis of NEC, but may prove useful when abdominal radiographs are unclear. A contrast enema in an infant with NEC may display mucosal irregularity and edema (10).

The differential diagnosis of NEC includes systemic and intestinal infections, congenital intestinal obstruction (e.g., volvulus, pyloric stenosis, ileal atresia, Hirschsprung's disease), neonatal appendicitis, spontaneous bowel perforation, and pseudomembranous colitis or ecchymotic colitis (1,5,9).

Aggressive treatment is indicated in all suspected cases of NEC. Such measures include oral feeding cessation, nasogastric decompression, and intravenous fluid therapy. Systemic antibiotics, usually ampicillin or an anti-pseudomonas penicillin with an aminoglycoside, are administered following blood culture collection. Umbilical catheters should also be removed. Respiratory status, coagulation profile, and acid-base electrolyte balance should be carefully monitored. Abdominal radiographs may be taken every six hours and the patient's general condition assessed every 4-6 hours (6).

Early consultation with a surgeon is advised in all cases of NEC. Conservative treatment is insufficient in 20-40% of cases (9). Surgical procedures may include exploratory laparotomy, necrotic bowel resection, and external stoma diversion. Intraperitoneal drainage is another option that is often used on patients who may not be able to tolerate a laparotomy and resection (9). Indications for surgical intervention include failure of medical management, pneumoperitoneum (an indication of perforation), abdominal wall cellulitis, and signs of gangrenous intestine (e.g., fixed intestinal loop, ascites) (6). Mortality rates in NEC cases involving surgery range from 20-50% (9).

The elusiveness of the etiology of NEC has made it difficult to establish effective preventive measures. The use of total parenteral nutrition with slow progression to enteral feeding rather than a rapid enteral feeding protocol may be one such measure. Studies also suggest that dopamine and dobutamine may reduce the risk of NEC by improving mesenteric blood flow and cardiovascular function (9). The use of human breast milk, rather than formula, may reduce the incidence of NEC by providing phagocytic cells, lymphocytes, neutrophils, and IgA (6,8).

NEC outbreaks have been reported, and epidemic precautions and infection-control measures are indicated in a suspected outbreak. Prophylactic antibiotics have been employed in the past; however the possibility of developing resistant organisms has discouraged their routine use (8).

NEC has a recurrence rate of about 4% in infants (6). About 10% of patients will develop strictures due to scarring and fibrosis of the bowel (6). Even mild cases of NEC can result in strictures (10). Intestinal resection may lead to short bowel syndrome and the many complications associated with the prolonged use of parenteral alimentation such as central venous catheter related sepsis and thrombosis, and cholestatic jaundice (2). NEC may also lead to enterocolonic fistulas, possibly through the adherence of inflamed bowel to adjacent bowel segments or through a previously closed perforation (9).

Questions

1. True/False: The majority of patients with NEC have visible blood in the stool.

2. Which of the following has not been suspected as a risk factor for NEC?
   a. aggressive enteral feeding
   b. maternal infections during delivery
   c. dopamine administration
   d. umbilical vein catheters
   e. all of the above have been considered as risk factors

3. True/False: Prophylactic antibiotics are a commonly used measure to prevent NEC.

4. How is the reduced intestinal motility of premature infants thought to contribute to the development of NEC?

5. A premature infant is suspected to have NEC. Name three initial treatment measures that should be employed.

Related x-rays

Newborn radiographs: Available online at: www.hawaii.edu/medicine/pediatrics/neoxray/neoxray.html

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Answers to questions

1. False, an estimated 25% show visible bloody stool.
2. c. Dopamine may actually reduce the risk of NEC by increasing mesenteric blood flow.
3. False, the development of resistant organisms presently discourages routine prophylactic antibiotic use.
4. Reduced intestinal motility increases the chances of bacterial overgrowth.
5. Acceptable answers include: 1) oral feeding cessation, 2) nasogastric decompression, 3) intravenous fluid therapy, 4) systemic antibiotics, 5) umbilical catheter removal, 6) acid-base electrolyte balance monitoring, 7) early consultation with a surgeon.

Chapter IV.1. Prenatal Genetic Screening and Testing

Greigh I. Hirata, MD

Mrs. H is a 37 year old G1P0 with irregular menstrual periods. She presents to you early in her pregnancy for prenatal counseling. Her significant family history includes a brother with unexplained mental retardation and a niece with beta-thalassemia major. She is of mixed Asian/Caucasian ethnicity. Her husband and the father of the baby is a 49 year old African-American with no significant family history. She seeks advice with regards to prenatal screening for birth defects and/or prenatal testing.

This case brings up important issues regarding prenatal screening and testing. It must be remembered that screening tests are designed to identify a high risk population from the general population. Screening tests are generally inexpensive and noninvasive. Prenatal testing is designed to answer a specific question in a population at high risk. Definitive diagnostic testing is typically expensive and invasive.

A complete prenatal evaluation begins with a careful medical and family history. When used in conjunction with a thorough physical examination (ultrasound evaluation) and laboratory testing, the practitioner is better able to individualize the patient's risks and recommend the appropriate diagnostic tests.

In this section, we will discuss the appropriate steps in risk assessment beginning with the family history. One typically begins the assessment by asking questions regarding other family members. A pedigree is constructed which includes three generations; grandparents, uncles, aunts, cousins, parents and siblings of the proband (the index case), in this case the fetus. Significant information includes histories of birth defects, genetic diseases, unexplained stillbirths, and unexplained mental retardation. It is important to recognize combinations of abnormalities and illness and patterns of inheritance that may require referral to a geneticist for diagnosis and further evaluation.

Also significant is the ethnic background of both parents. Specific genetic diseases are much more common in certain ethnic groups. For example, southeast Asians and Mediterraneans are at risk for thalassemia and glucose-6-phosphate dehydrogenase deficiency, African-Americans are at risk for beta thalassemia and sickle cell disease, Ashkenazi Jews are at risk for Tay-Sachs disease and have a genetic predisposition to certain types of cancers, and northern Europeans are at risk for cystic fibrosis. Screening tests for the carrier status are readily available for each of these disorders and should be performed prior to any prenatal diagnostic test if the couple is at risk.

The most obvious screening test for fetal aneuploidy is maternal age. This association has been well characterized and has lead to the recommendation that invasive genetic testing be offered to any women 35 years or older at the expected date of delivery. Although every pregnant women is at risk for aneuploidy, this age cutoff offers the most efficient and effective method for determining candidates for prenatal testing. Advanced maternal age is also a risk factor for increased maternal morbidity and mortality primarily related to increase rates of pregnancy complications such as preeclampsia and gestational diabetes. Pregnancy wastage, unexplained stillbirths and other adverse perinatal outcomes are also increased. As women increasingly delay childbearing to later years, clinicians should become aware of these risks to better counsel their patients.

Advanced paternal age (45 years or greater) places the fetus at risk for new autosomal dominant mutations. Examples of these genetic disorders include achondroplasia, Marfan syndrome and certain types of osteogenesis imperfecta. Unfortunately the exact occurrence risk is unknown and invasive prenatal testing are not available for many of these genetic disorders.

One of the greatest breakthroughs in prenatal diagnosis has been the emergence of maternal serum screening in the identification of pregnancies at risk for chromosomal aneuploidy and birth defects. Originally designed as a test for spina bifida and ventral abdominal wall defects, these tests are performed at 15-20 weeks gestation.

Abnormal levels of the maternal serum markers human chorionic gonadotropin (hCG), alpha-fetoprotein (aFP), and unconjugated estriol (uE3) are associated with trisomy 21 and 18. Moreover, these markers are predictive of aneuploidy independent of maternal age related risks. This has lead to the development of calculated individualized risk for these specific aneuploidies (utilizing maternal age and maternal serum biochemical markers). This test, also known as the triple screen, is rapidly replacing maternal age alone as an indicator for invasive genetic testing. It has enabled clinicians to identify women at risk for aneuploid fetuses who are less than advanced maternal age (< 35 years old). Conversely, many women greater than 35 years old have been reassured by risk reduction and thus have avoided placing the pregnancy at risk with invasive genetic testing. The maternal serum screening is also useful in identifying those pregnancies at risk for specific birth defects such as neural tube defects and ventral abdominal wall defects. In this case, the maternal serum marker aFP is elevated. Typically hCG and uE3 are unaffected.

Other etiologies for abnormal test results include fetal demise, multiple gestations, and incorrect gestational age determination. By identifying these problem pregnancies and evaluation by ultrasound, clinicians are better able to intervene or anticipate pregnancy complications. In the absence of recognizable explanations for an elevated maternal serum aFP level, there has been a noted increased risk for adverse perinatal outcomes such as preterm birth, intrauterine growth retardation, oligohydramnios and stillbirth. Unfortunately treatment protocols have been unsuccessful in significantly improving the outcomes of these high risk pregnancies.

The future of maternal screening involves earlier identification of pregnancies at risk either by serum screening or ultrasound as well as noninvasive methods for prenatal diagnosis. We will now explore tests which will become clinically available in the not too distant future. Researchers are busy investigating promising new maternal serum markers applicable earlier in pregnancy. Like hCG, aFP, and uE3, these markers are independent predictors of aneuploidy, primarily trisomy 21. The utilization of these markers is estimated to increase sensitivity rates by approximately 5%. In the near future, maternal age in conjunction with serum markers such as inhibin, pregnancy associated plasma protein-A (PAPP-A), and urinary human chorionic gonadotropin-core may be used alone or in combination as screening tools in pregnancy. Nuchal translucency (significant swelling of the nuchal area seen on ultrasound) occurs in approximately 70 % of aneuploid fetuses at 10-14 weeks gestation independent of maternal age risks. Evaluation of early gestations by sonography may identify these fetuses at risk. The promising future direction of early pregnancy screening will probably involve a combination of nuchal translucency, maternal age, and serum screening utilizing beta-hCG and PAPP-A in identifying these abnormal gestations.

Fetal cells normally appear in the maternal circulation. Because of breakthroughs in isolating these cells from the maternal circulation and genetic technology enabling testing minute samples of tissue, noninvasive prenatal diagnosis is a real future possibility. Prenatal diagnosis would therefore be possible without placing the fetus at risk (i.e., an amniocentesis may not be necessary in most instances). Clinical trials are currently underway investigating the feasibility of this new technology.

Ultrasonography has revolutionized the field of prenatal diagnosis since its introduction into clinical medicine in the 70's. The previously visually inaccessible uterus has been revealed by this noninvasive technology. It is important to realize that sonography can be

used not only as a screening tool but also a diagnostic tool. The value of ultrasound as a screening tool is controversial most likely because it is highly dependent on the skill of the examiner.

Prenatal testing involves invasively obtaining samples from the fetus or fetal tissues. The cells can then be analyzed for a variety of tests including karyotype analysis, molecular DNA analysis, and chemistries and cultures. We will now explore the different prenatal testing procedures that are currently available.

Amniocentesis is generally performed at 15-20 weeks gestational age. This test involves sonographic localization of the placenta, fetus and amniotic fluid. Under ultrasound guidance, a spinal needle is inserted percutaneously into the amniotic sac withdrawing approximately 20 cc's of amniotic fluid. Within this fluid, fetal cells from the fetal skin, urinary system and amniotic membranes are spun down and collected. The cells are then grown in culture for approximately 5-6 days and arrested in the metaphase of the cell replication cycle. After fixation and staining, the chromosomes are identified and counted to assess the number and gross structure. Typically, humans have 22 pairs or autosomes and two sex chromosomes for a total of 46 chromosomes. As with any invasive tests, there is a risk for miscarriage of approximately 1:200-300 procedures performed.

Chorionic villus sampling can be accomplished in the first trimester by sampling the placenta either transcervically or transabdominally. Since the placenta is fetal in origin, karyotype analysis of the placental cells will most often accurately reflect the fetal chromosomes. This test is typically performed at 10 ½ to 13 weeks gestation. The major advantage to this procedure is the earlier gestational age at the time of diagnosis. The draw back is a slightly increased risk for miscarriage of approximately 1:75-100 procedures performed.

Percutaneous umbilical blood sampling (PUBS) of fetal blood is sometimes required to evaluate fetal anemia, fetal infection, and rapid fetal karyotype. This procedure allows direct evaluation of fetal blood and serum. The procedure is performed much like that of an amniocentesis under ultrasound guidance. The needle is directed to the umbilical cord and blood removed directly from the fetal blood vessels. Because the target is much smaller, skill at imaging the vessel and directing the needle is an absolute requirement. Blood withdrawn can be analyzed much like any other blood sample. In addition, since the white blood cells in the fetal circulation are actively dividing, karyotype analysis is accomplished much quicker, often without requiring many days of cell growth. This procedure can be performed as early as 16 weeks gestational age. The miscarriage risk for this procedure is approximately 1%.

Questions

1. Pertinent family history includes all of the following except:
    a. Ethnic background
    b. Family members with mental retardation
    c. Family members with birth defects
    d. Step parents

2. True/False: The risk of aneuploidy such as trisomy 21 only exists in women over 35 years old.

3. Increased paternal age is associated with which of the following:
    a. Aneuploidy
    b. Increased perinatal mortality and morbidity in otherwise normal fetuses
    c. New dominant genetic mutations
    d. Pregnancy medical complications

4. Midtrimester maternal serum screening utilized levels of these analytes (biochemical markers) except:
    a. human chorionic gonadotropin
    b. alpha-fetoprotein
    c. fetal cortisol
    d. unconjugated estriol

5. Potential confounding factors in the analysis of maternal serum screening include all of the following except:
    a. Fetal demise
    b. Wrong dates
    c. Multiple gestation
    d. Male fetus

6. Unexplained elevated maternal serum alpha-fetoprotein levels portends higher risk for the following perinatal outcomes except:
    a. Oligohydramnios
    b. Stillbirth
    c. Gestational diabetes
    d. Preterm delivery

7. In addition to the detection of aneuploid fetuses, maternal serum screening aids in all of the following except:
    a. Detection of multiple gestations
    b. Determining paternity
    c. Detection of wrong estimation of gestational age
    d. Identifying patients at risk for adverse perinatal outcome

8. Future maternal screening may involve the following analytes except:
    a. Progesterone
    b. Inhibin
    c. Pregnancy Associated Placental Protein A
    d. Urinary human chorionic gonadotropin core

9. True/False: The nuchal translucency measurement in the 10-13 week gestation as a predictor of aneuploidy is independent of maternal age:

10. Prenatal testing procedures currently include all of the following except:
    a. Amniocentesis.
    b. Fetal cells in the maternal circulation.
    c. Chorionic Villus Sampling.
    d. Percutaneous Umbilical Blood Sampling.

Answers to questions
1.d, 2.false, 3.c, 4.c, 5.d, 6.c, 7.b, 8.a, 9.true, 10. b

Chapter IV.2. Congenital Anomalies and Teratogenesis
Greigh I. Hirata, MD

Ms. T is a 17 year old G3P0Tab2 who presents in her 18th week of pregnancy seeking prenatal counseling. She states she has been a type II diabetic under poor control for 4 years and does not regularly take her oral hypoglycemic agent. She is also taking lithium for a manic disorder and has been drinking alcohol regularly for the past 6 months. She is undecided on her commitment to this pregnancy.

This example demonstrates that there are multiple opportunities to effect fetal development. Medical illnesses, prescription medication and environmental exposures play important roles in the pathogenesis of birth defects. In this section we will review the broad topic of teratogens and congenital anomalies.

Physiologic Basis of Birth Defects

The development of birth defects is greatly dependent on the gestational age, nature of the teratogens and the intensity and duration of exposure. The reader is strongly encouraged to review human development, particularly embryology as it relates to organogenesis, to better understand how and when environmental factors may influence fetal development. Organ systems differ in the timing and duration of formation, which results in marked differences in susceptibility. For example, the cardiovascular system undergoes a lengthy and complex developmental phase which probably explains why this organ system has the highest incidence for birth defects. Also as general rule, significant early insults (less than 8 gestational weeks) result in spontaneous miscarriages, whereas exposure later in the gestation (typically after organogenesis or approximately 14-16 weeks gestation) has less of an effect. There are, however, many exceptions to these basic rules.

It is essential to understand the pathophysiologic mechanisms for fetal mal-development, which may be divided into malformation, deformation, disruption or dysplasia. A malformation is commonly defined as a single localized poor formation of tissue that initiates a chain of subsequent defects (1). Anencephaly, for example, is a result of a failure of closure of the anterior neural tube prior to 26 days of fetal life which ultimately results in the degeneration of the forebrain. The recurrence risk for malformations generally range from 1 to 5 per cent. In comparison, a deformation is a result of extrinsic mechanical forces on otherwise normal tissue. This is illustrated in the characteristic pattern of abnormalities including the abnormal facies, pulmonary hypoplasia, and limb contractures that result from prolonged oligohydramnios, either secondary to renal agenesis (Potter syndrome) or premature rupture of membranes (Potter sequence). A disruption results from an extrinsic insult, which destroys normal tissue altering the formation of a structure. The patterns of findings that result from amniotic bands and limb strangulation (a condition in which torn amniotic tissue strands surround a portion of the of body, often digits or extremities, resulting in deep grooves or amputations) are good examples of a disruption type birth defect. Finally, if the primary defect is a lack of normal organization of cells into tissue, a dysplasia will result. This is best illustrated by the pattern of bony abnormalities found in achondroplasia where a defect in the gene encoding fibroblast growth factor receptor 3 results in abnormal cartilage formation.

It is also important to recognize the differences between a "syndrome" and an "association". Syndromes are typically a result of a single genetic abnormality whereas associations are nonrandom collections of birth defects, which may have resulted from a number of genetic factors. This is illustrated when one compares Down syndrome (a result of an extra copy of chromosome 21) with VATER Association (a nonrandom association of vertebral anomalies, imperforate anus, and esophageal atresia with tracheoesophageal fistula). The understanding of these pathophysiologic mechanisms and nomenclature is important in the study of birth defects.

Medical Conditions Affecting Fetal Development

Medical illnesses are seldom thought of as fetal teratogens. This is not the case in the following examples demonstrating how important pre-conceptual counseling is in prevention of birth defects.

Diabetes mellitus: It is well known that pre-gestational and early gestational glucose control greatly influence the rate of miscarriage and fetal anomalies. In a study performed by Hanson et al (2), hemoglobin A1c levels for those women seeking prenatal care were linearly correlated with the rate of miscarriage and anomalies. Moreover, in a summary of 11 studies by Gabbe (3), the incidence of birth defects were 2.5% in those women seeking glucose control pre-conceptually versus 7.8% in those women presenting after conception. The hemoglobin A1c level at 14 weeks, reflecting glycemic control 3-4 weeks prior, is predictive of the rate of fetal anomalies. A hemoglobin A1c level >8.5% confers a risk of birth defects of approximately 22% versus 3.4% in women with A1c levels <8.5% (4).

The pattern of anomalies secondary to diabetes are characteristic. Infants of diabetic mothers are particularly prone to defects in the cardiovascular system, central nervous system and skeletal system. The relative risk for cardiac anomalies is 4.3 times higher compared

with normal glycemic controls (5). The relative risk for central nervous system anomalies such as anencephaly (3.3 RR) and spina bifida (1.4 RR) are also increased (5). The rare disorder, caudal regression syndrome is almost pathognomonic (RR 175) for maternal diabetes mellitus (5).

The goals of pre-conceptual treatment are euglycemia and avoidance of glycemic fluctuations. Pre-prandial capillary glucose should be <110 mg/dl with the one-hour post-prandial levels <140 mg/dl. Because of these strict goals and concerns regarding transplacental exposure, oral hypoglycemic agents are deemed inadequate. The optimal treatment would involve preconceptual counseling and glycemic control at least 3 months prior to conception.

Seizure Disorders: Maternal seizure disorders are another example of an illness associated with birth defects. There is some evidence suggesting that epilepsy in and of itself may be teratogenic. However, the pattern of abnormalities encountered with this disease is not well defined. Of major concern is the potential for teratogenesis because of exposure to anti-seizure medications. Most anticonvulsants have significant risk for birth defect formation. However, the ultimate goals of any treatment are first and foremost, control of seizure activity. Moreover, if at all possible, monotherapy is preferred over polytherapy.

The fetal effects of valproic acid include increased risks for specific craniofacial abnormalities, cardiovascular defects and neural tube defects. It is estimated that the risk for neural tube defects is 1-2%. Since valproic acid interferes with folic acid metabolism, patients on this medication may benefit from preconceptual folic acid administration.

Phenobarbital may lead to fetal withdrawal in the neonatal period. The possibility of a fetal barbiturate syndrome is currently controversial. Babies exposed to this medication in utero have be found to be relatively vitamin K deficient leading to the recommendation of maternal vitamin K administration at least one month prior to parturition.

The hydantoin (phenytoin) syndrome consisting of the constellation of growth and performance delays, cranio-facial abnormalities, and hypoplasia of the nails and distal phalanges has been well recognized. Like phenobarbital, vitamin K deficiency has been observed in these neonates and therefore maternal vitamin K administration is recommended one month prior to birth is recommended.

Carbamazepine is generally well tolerated and safe in pregnancy. There is an estimated 1% risk for neural tube defect which may be amenable to reduction by preconceptual administration of folic acid. There has also been a suggestion of a pattern of malformations similar to that seen with phenytoin exposure.

Teratogens

In this section we will review a compilation of some of the common teratogens. Remember that the risk for the fetus is greatly dependent on the timing of exposure, duration and intensity of the agent, and genetic susceptibility. For a complete list of teratogens and potential fetal effects, the reader is referred to resources listed in the reference section of this chapter.

Coumarin (coumadin, warfarin) is a vitamin K antagonist used for anticoagulation which has been linked to a well described pattern of malformations including nasal hypoplasia, intrauterine growth retardation, developmental delay and a characteristic stippling of the bone epiphyses. The incidence of this pattern is estimated to be 10% if exposure occurs within the first trimester of pregnancy.

Lithium is commonly used in the treatment of bipolar or manic disorders. Exposure to this medication in the first and early second trimester of pregnancy is associated with a 1-5% risk of congenital heart defects, particularly Ebstein anomaly.

Angiotensin-converting enzyme (ACE) inhibitors, a class of antihypertensive agents, is associated with renal tubular dysplasia/anuria, oligohydramnios, intrauterine growth retardation, and defects of ossification when the fetus is exposed in the late second and third trimester of pregnancy.

Fetal exposure to retinoic acid, such as isotretinoin (Accutane) is associated with characteristic craniofacial abnormalities, central nervous system defects, cardiovascular abnormalities and mental retardation. The estimated risk is 35% if taken beyond the 15th day following conception. Similar types of birth defects are also seen in women who ingest large amounts of other forms of vitamin A.

Maternal pyrexia is not commonly thought of as a fetal teratogen but there are a number of experimental and observational studies suggesting otherwise. In laboratory guinea pigs, Edwards et al has shown that heat exposure to fetal pup at a critical stage in development has induced a number of neurologic developmental abnormalities and vascular disruption defects such as bowel atresias (6). In humans, maternal exposure to hot tubs significantly increased the incidence of neural tube defects (relative risk 2.9, confidence interval 1.4-6.3) over nonexposed controls (7).

Perhaps the most common avoidable human teratogen is alcohol. It is estimated that the risk for fetal alcohol syndrome is 10% if exposed to 1-2 drinks per day. The incidence increases to 40% if the exposure increases to 6 drinks per day. The syndrome consists of small for gestational age/intrauterine growth retardation, characteristic craniofacial abnormalities, congenital heart defects, and developmental delays. A greater number of infants are born with fetal alcohol effect, a clinically milder but similar form of fetal alcohol syndrome. This uncertainty has prompted the recommendation that there is no safe amount of alcohol consumption during pregnancy.

Exposure to illicit recreational drugs such as amphetamines and cocaine is theorized to cause defects in prosencephalic development or neuronal migration resulting in abnormalities such as agenesis of the corpus callosum and brain clefts. It is also hypothesized that the incidence of fetal vascular accidents is increased resulting in cerebral infarcts, intracerebral hemorrhage, and intestinal atresias and limb reduction defects. Late exposure has been associated with intrauterine growth retardation, preterm delivery and placental abruption.

Genetic basis of fetal teratogen susceptibility

It has long been observed that exposure to many teratogens results in a wide range of effects. It has been speculated that certain individuals carry a genetic susceptibility. These are two examples of how genetic predisposition may interact with the environment and result in the formation of a birth defect.

In epoxide hydrolase deficiency, (this enzyme is critical in the metabolism of anticonvulsant medications such as phenytoin), it has been speculated that a deficiency in this enzyme may result in an accumulation of oxidative metabolites. Bueher, et al has found that in 19 women on phenytoin, four fetuses with low levels of enzyme activity were found to have clinical features of the phenytoin embryopathy whereas 15 fetuses similarly exposed with enzyme activity above 30% of controls (i.e., more normal enzyme levels) were normal (8).

Methylenetetrahydrofolate reductase (MTHFR): A common abnormal variant of this enzyme leads to elevation of homocysteine levels through inhibition of the folate-mediated remethylation of that compound. It is very common, with an estimated 30-40% of the general population heterozygous and 10% homozygous for this mutation. There is evidence that elevated homocysteine levels may be teratogenic in laboratory animals and humans. It is speculated that fetuses homozygous for the MTHFR mutation born to folate deficient mothers are at increased risk for defective neural tube formation.

Questions

1. Achondroplasia is an example of a:
    a. Malformation
    b. Deformation
    c. Disruption
    d. Dysplasia

2. Amniotic Band Syndrome is an example of a:
    a. Malformation
    b. Deformation
    c. Disruption
    d. Dysplasia

3. An "association" is a:
    a. result of a single genetic abnormality.
    b. nonrandom collection of birth defects.

4. Anencephaly is an example of a:
    a. Malformation
    b. Deformation
    c. Disruption
    d. Dysplasia

5. A significant fetal insult in the first trimester of pregnancy most commonly results in a:
    a. severe birth defect
    b. minor birth defect
    c. no birth defect
    d. miscarriage

6. The most common organ systems involved with diabetic embryopathy include:
    a. the cardiovascular system
    b. the central nervous system
    c. the spinal system
    d. all of the above
    e. none of the above

7. The safe level of alcohol consumption in pregnancy is:
    a. less than 2 drinks per day
    b. less than 6 drinks per day
    c. there is no safe level

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Answers to questions

1.d, 2.c, 3.b, 4.a, 5.d, 6.d, 7.c

Chapter IV.3. Common Chromosomal Disorders
Julie Won Ireland, MD

A two day old male infant is referred from a community hospital for bilious vomiting and a heart murmur. The baby was born at 37 weeks gestation to a G4P3 39 year old woman who had no prenatal care.

Exam: VS T37.1 (ax), P150, R45, BP 75/50, oxygen saturation 99% in room air. Height, weight and head circumference are at the 50th percentile. He appears jaundiced, and has a flat facial profile; short, upslanting palpebral fissures; a flat nasal bridge with epicanthal folds; a small mouth with protruding tongue; and single palmar creases. His lungs are clear to auscultation. His heart is tachycardic with a loud holosystolic murmur. His abdomen is non-distended. Generalized hypotonia is present.

An abdominal radiograph shows a "double-bubble sign". Duodenal atresia is suspected. A nasogastric tube is placed and IV fluids are administered. He later undergoes a duodenoduodenostomy. An echocardiogram demonstrates a ventricular septal defect, which is medically managed. A chromosomal abnormality is suspected and a karyotype is done. Trisomy 21 is diagnosed.

This chapter deals with some of the more common chromosomal abnormalities encountered in clinical practice. While the infant described above has trisomy 21, or Down syndrome, other disorders of chromosomes include trisomy 18 (Edwards syndrome), trisomy 13 (Patau syndrome), XXY (Klinefelter syndrome), 45X (Turner syndrome), Noonan syndrome, XYY syndrome and Fragile X syndrome.

Trisomy 21 (Down syndrome)

Dr. John Langdon H. Down first described a cluster of mentally retarded patients in an England asylum in an essay, "Observations on an Ethnic Classification of Idiots," in 1866. It was not until the 1950s that an extra 21st chromosome was found to be responsible for what was to become known as Down syndrome. The incidence is 1 in 600-800 births. The sporadic form has a higher frequency with advanced maternal age. In mothers less than 25 years of age, the risk is 1 in 2000 births and climbs to 1 in 20 births for mothers over age 40. All patients with Down syndrome have three copies of chromosome 21. In 95% of patients, there are 47 chromosomes with trisomy of chromosome 21. In about 5%, there are 46 chromosomes, with an abnormally translocated 21st chromosome. Robertsonian translocations involve the transfer of chromosomal material from 21 to usually chromosome number 13, 14, or 15. The Down phenotype occurs when even a small, but critical piece of the long arm of chromosome 21 is trisomic. Carriers of a Robertsonian translocation are usually phenotypically normal, but are at increased risk for miscarriages and chromosomally abnormal children. Another cause is a 21q/21q translocation. This is rare, but significant because a carrier parent only has one 21st chromosome (the translocated chromosome with double the genetic material). When this chromosome is passed on, all of the offspring will have trisomy 21. An example of this is a mother who had this translocation and had four children with Down syndrome. Milder phenotypes may be seen when patients are mosaic for trisomy 21. This happens when nondisjunction occurs early in embryonic development as a mitotic error.

Affected patients have a characteristic facies including epicanthal folds, a flat nasal bridge, small mouth, protruding tongue with microcephaly and a flat occiput. Other features may include a high arched palate, a single palmar crease (Simian crease). The pupils may have light smudgy opaque Brushfield spots. At birth, patients are often hypotonic and have a higher incidence of other types of malformations. Cardiac anomalies are present in 33-50% and include endocardial cushion defects and ventricular septal defects. Gastrointestinal anomalies can include duodenal atresia and Hirschsprung's disease. Later in life, hypothyroidism and leukemia can occur, and there is an increased susceptibility to infections. Atlanto-occipital instability may be present in a few and is a concern when intubating these patients. A pneumonic for remembering the major complications found in Down syndrome patients is using the word VALIDATE as follows: VSD, Atlanto-occipital instability, Leukemia, Immunodeficiency, Duodenal atresia, Alzheimer's disease, Thyroid dysfunction, and Endocardial cushion defects.

There is no treatment for the trisomy itself, so therapy is directed towards other complications present, such as cardiac and gastrointestinal anomalies, thyroid dysfunction, and infections. Their IQ is usually about 50-75, at best they function at a sixth grade level, and few are severely retarded. These children are placed in infant stimulation programs, enrolled in special education classes, and later given occupational training to help them become more independent and a functioning part of society. It is very important to counsel parents who have one child with Down syndrome about the risk of having a second affected child. The risk of recurrence is 1% in otherwise low risk moms and if the parent is not a translocation carrier. Obstetric screening tests can identify some pregnancies at risk, so that fetal chromosome testing can be offered. Involvement in compassionate support groups should be encouraged to the parents.

Trisomy 18 (Edwards Syndrome or Trisomy E)

Infants with trisomy 18 are severely affected and usually die in the first week of life. Less than 10% of patients survive beyond twelve months and are profoundly mentally retarded. The cause of this syndrome is usually full trisomy for chromosome 18. The incidence is 1 in 4000-8000 births, with a 3:1 predominance of affected females to males. The risk increases with maternal age. The recurrence risk is very low based on the observation that most affected children die in utero. Patients with trisomy 18 mosaicism have a less severe clinical expression and longer survival depending on the degree of mosaicism. Partial trisomy 18 varies in its clinical picture from mild mental deficiency and improved survival to being indistinguishable from full trisomy 18. This depends on the extent and which part of the chromosome is affected.

Numerous malformations have been reported in trisomy 18. These infants have a characteristic head shape and facial features, such as a prominent occiput, low-set ears, and micrognathia. The hands are often clenched with the index finger overlapping the third finger. Dysmorphic joints produce this typical finger position. Deformities of the lower extremities include hypoplastic nails of the feet, malaligned toes and "rocker-bottom feet", where the calcaneus is prominent. Heart defects, such as ventricular septal defect, patent ductus arteriosus or atrial septal defect, are found in at least 50% of these patients. They also have a short sternum with small nipples.

Supportive care is the treatment for this syndrome. Genetic counseling is indicated. Chromosomal studies should be done to determine translocation cases. The recurrence risk for full 18 trisomy cases is less than 1% because most die in embryonic or fetal life. Some children with trisomy 18 have reached adulthood. Heart failure or pneumonia are some of the complications that often cause death.

Trisomy 13 (Patau Syndrome or Trisomy D)

The constellation of findings in this condition have been described as far back as the 1600's. Klaus Patau and his colleagues were the first to attribute the syndrome of trisomy for chromosome 13 by cytogenetic analysis in 1960. The cause of this syndrome is usually trisomy for chromosome 13. Its overall incidence is 1 in 12,000 births, but the risk increases with maternal age. The recurrence rate is

very low, except for the parent who has a balanced translocation. Patients with trisomy 13 mosaicism have been described and usually have a milder phenotype depending on the degree of mosaicism.

Patients are severely affected and often die in infancy. The median survival has been reported as two and a half days. Surviving infants have severe mental retardation and may have midline CNS defects, incomplete development of the forebrain, apneic episodes and EEG abnormalities. Bilateral cleft lip and palate are common. Microcephaly, microphthalmia, and deafness may also be found. Lethal cardiac anomalies are found in 80% of patients, with VSD being the most common. PDA, ASD, dextroposition, and valvular abnormalities can also occur. Disorders of the extremities may include a single palmar crease (Simian crease). Polydactyly, particularly of all extremities, strongly suggests trisomy 13. Overlap of the middle and ring fingers are seen.

Treatment is supportive. Prevention by genetic counseling is indicated. Critical decisions in regards to extensive therapy and resuscitation measures in a severely affected infant must be decided at birth. Those affected usually die in infancy; very few live to become adults. Children who survive are severely retarded and are rarely able to suck. They fail to thrive and have seizures.

Klinefelter Syndrome (47 XXY)

Harry Fitch Klinefelter worked with Dr. Fuller Albright in clinical endocrinology when he saw his first patient, who was a young man with small testes and gynecomastia. During his fellowship, he encountered 8 other patients with similar findings and described Klinefelter syndrome in 1942. Klinefelter syndrome affects 1 in 1000 newborn boys and is caused by an extra X chromosome from meitotic nondisjunction. The incidence is 1% among the mentally retarded and 3% among males seen at infertility clinics. In 54% of the patients, the extra X chromosome comes from the mother and in the other 46%, the extra X chromosome comes from the father. Maternal age, but not paternal age is often advanced. The most common chromosomal pattern is 47,XXY. Others have mosaic patterns: 46,XY/47,XXY; 46,XY/48,XXYY; or 46,XX/47,XXY. These patients tend to have milder phenotypes. Children with mosaicism have a better prognosis for fertility and virilization. In chromosome variants with multiple X chromosomes (XXXY and XXXXY), the clinical manifestations are much more severe. In general, the mental and physical abnormalities associated with Klinefelter syndrome worsen as the number of X chromosomes increase.

The characteristic findings of Klinefelter syndrome usually do not become apparent until after puberty. They have a eunuchoid habitus; usually tall, slim and underweight, with long legs. One third have gynecomastia and they have less facial hair. Their gonads are small and soft, and the phallus tends to be smaller than average. The seminiferous tubules are atrophied because of excess gonadotropin. There is hyperplasia of the Leydig cells, producing azoospermia and infertility. Cryptorchidism may occur in some patients. Hypogonadism becomes recognized after puberty when the testicles fail to grow and develop normally. This is usually the time when the diagnosis is suspected. Pubertal development may be delayed. These patients tend to have learning and psychosocial problems. They have normal to borderline IQ, with a mean IQ of 90. In boys with mental retardation, learning disabilities or adjustment problems at school, Klinefelter syndrome should be a consideration. Later in life, these individuals are at higher risk to develop diabetes mellitus. There is also an increased incidence of cancer of the breast, varicose veins, and pulmonary disease.

Chromosomal analysis should be done to confirm the diagnosis of Klinefelter syndrome. In males younger than 10 years of age, they have normal levels of FSH and LH and respond appropriately to GnRH and hCG. In late adolescence, testosterone levels decrease, and gonadotropins increase. In adults, urinary excretion of gonadotropins is high, with levels comparable to those seen in post menopausal women. Gynecomastia is a result of an elevated estradiol to testosterone ratio. In the management of Klinefelter syndrome, testosterone replacement therapy should start at 11 to 12 years of age, if testosterone levels are deficient and gonadotropin levels become elevated. With early recognition and diagnosis, treatment can be initiated to allow a more normal maturation for the affected male, but infertility cannot be reversed.

Turner Syndrome (45X)

In 1938, a series of young women with failure of sexual maturation, short stature, and neck webbing were reported by Henry Turner. He believed this was due to a defect in the anterior pituitary gland. It was not until 1959, when the absence of the X chromosome was first described by Charles Ford. The incidence is 1 in 2500 live female births, 95% of 45X fetuses die in utero. About 50% of patients apparently have the full monosomy 45,X, the others all have detectable mosaicism. About 2/3 retain the maternal X and 1/3 have the paternal X. Advanced maternal age is not a factor in this syndrome. Only one X is normal and functioning; the other X is not present or is missing a part of its chromosome by structural abnormality, deletion or translocation. Mosaicism 45,X/46,XX or 45,X/46,XX/47,XXX may also be present. 10% of Turner mosaics have a Y chromosome, 45,X/46,XY is seen. The presence of the Y chromosome increases the risk of gonadoblastoma. Milder phenotypes are usually seen in those without the full monosomic karyotype.

The characteristic features include a triangular face, small mandible, prominent ears, webbed neck, low posterior hair line, shield chest with wide set nipples, cubitus valgus (increased carrying angle of the elbow), and short stature. Sometimes short stature may be the only clinical finding present in a young girl. Their average adult height is about 143 cm (4 ft., 8 in.). In most of these girls, secondary sexual characteristics are absent. They have amenorrhea and are infertile due to ovarian dysgenesis. Intelligence is usually normal, but they may have a learning disability. These patients may have cardiac defects; 30-50% have bicuspid aortic valve, and 10-20% have coarctation of the aorta. Other cardiac complications include aortic stenosis, aortic dissection and idiopathic hypertension. Urinary tract malformations are found with a higher frequency in these patients. Most common presentations include a horseshoe kidney, kidney located in the pelvis, double collecting system, or absence of a kidney.

Growth hormone alone or in combination with anabolic steroids has been successful in managing these patients. This is still very controversial. Opponents claim that growth hormone accelerates growth, but does not increase adult height. Therapy should begin when the height of the patient drops below the 5th percentile on the growth curve. For those who are deficient in estrogen and progestin, long term replacement therapy is required for development of secondary sexual characteristics and initiation of the menstrual cycle. As for all post-menopausal women, these women especially need hormonal therapy, in combination with calcium supplementation and exercise, to help prevent osteoporosis. Rarely, spontaneous puberty and menses can occur and pregnancy is possible. There is an increased risk of giving birth to a child with chromosomal or congenital anomalies. Genetic counseling and a medical work up are required. Support groups can be of much benefit. These women can become independent and lead productive lives. Most die in utero, but for those who survive, the average age of death is 69. Increased mortality can primarily be attributed to cardiovascular disease.

Noonan Syndrome

This syndrome resembles Turner syndrome and occurs in males and females. The occurrence is often sporadic, but an autosomal dominant inheritance has been reported. A gene for this disorder has been mapped to chromosome 12q; although not in every family, suggesting that other loci may be involved.

The clinical manifestations are short stature, short or webbed neck, shield chest and pectus excavatum or carinatum. They have a characteristic facies; epicanthal folds, ptosis, hypertelorism, downslanting palpebral fissures, and low or abnormal ears. Interestingly, their facies can normalize with age. The most common cardiac abnormality is pulmonary valve stenosis, but they can also have atrial septal defects, left ventricular hypertrophy, or patent ductus arteriosus. Males may have cryptorchidism, small penis, and hypogonadism. However, in males without cryptorchidism, fertility is normal. Fertility is also normal in females. About 25% of affected patients have some degree of mental deficiency.

There is no specific treatment. Genetic counseling should be offered to parents regarding the recurrence risk.

XYY Syndrome

In random newborn males, the incidence of the 47,XYY karyotype is 1 in 1000. In some prison populations, the incidence is 1-2 %. In institutionalized men or juvenile delinquents taller than 6 feet, 10% have XYY syndrome. Most 47, XYY males are phenotypically normal, however variable, non-specific characteristics may be seen. Stature tends to be tall, and patients may have large teeth and severe nodulocystic acne. They are not well coordinated or strong relative to their large size. Some males have anti-social behavior. They may be impulsive, hyperactive, have poor social skills, and low self esteem. They were once stereotyped as being violent and aggressive. However, longitudinal studies suggest that aggressive behavior is usually not a problem, and they learn to control their anger by the time they become young adults. These males have a normal to low IQ, and 50 % have a learning disability. The majority of patients are fertile. Their sperm may have 23,X, 23,Y, 24,XY or 24,YY, so the syndrome can recur. However, they usually have children with normal chromosomes.

XYY syndrome is diagnosed by karyotype. There are no consistent clinical findings. There is no treatment for this syndrome. In general, affected children are normal. However, behavioral modification is necessary in dealing with the hyperactivity and aggressiveness that may be seen during childhood. The majority are well-adapted citizens.

Fragile X Syndrome

The syndrome was first described by Martin and Bell in 1943, though the fragile site on the X chromosome was reported in 1969 by Lubs. It occurs in 1 in 1000 males. This disorder is caused by an expanded trinucleotide repeat (CGG) in the FMR-1 gene on the X chromosome with X-linked inheritance. When cells, from patients with this disorder, are cultured in a certain medium deficient in folate or thymidine, the fragile site can be visualized. The normal allele repeat range is 6-40. The intermediate allele repeat range is 41-60 repeats (most are stably inherited), and the premutation allele repeat range is 61-200 repeats. Carriers of the premutation are usually phenotypically normal and not at increased risk for retardation. Females who carry this premutation may pass down an expanded version resulting in full expression of the phenotype in males and variable phenotypic expression in females. The severity correlates with the increase in size of the repeat sequence. The full mutation (disease causing) repeat range is greater than 200 repeats. Other disorders that are caused by expanded trinucleotide repeats include Huntington disease, myotonic dystrophy and Friedreich ataxia.

Physical abnormalities in males with fragile X syndrome include large ears, a large jaw and large, soft testicles. Connective tissue dysfunction, mitral valve prolapse and dental crowding can also be found. Cluttered speech, autism, hyperactivity and mild to severe mental retardation are common. Females with fragile X syndrome (usually heterozygous) tend to have a less severe clinical expression and only 1/3 have mental retardation.

Treatment and management includes supportive care. Genetic counseling is important in prenatal and postnatal diagnosis of fragile X syndrome. Clinical expression is different depending on which parent transmits the gene. DNA analysis helps to identify full mutations as well as premutation carriers. The life expectancy is normal.

Questions

1. What chromosomal disorder(s) can present with bilateral cleft palate, cleft lip and a ventricular septal defect?
2. This syndrome presents with a prominent occiput, clenched fists and "rocker bottom feet". What are 2 complications that can cause death in these children?
3. Name 4 disorders associated with a trinucleotide repeat?
4. Name 8 complications of Down syndrome.
5. What is the etiology of infertility in women with Turner syndrome?
6. What causes gynecomastia in males with Klinefelter syndrome?
7. Which terminology below (one or more) for trisomy 21 is (are) incorrect?
    a. Down syndrome
    b. Downs syndrome
    c. Down's syndrome
    d. Mongolism
    e. Trisomy 21

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Answers to questions

1. Trisomy 13, Trisomy 18
2. Trisomy 18. Heart failure and pneumonia
3. Fragile X syndrome; Huntington disease; Friedreich ataxia; and myotonic dystrophy
4. VALIDATE: VSD, Atlanto-occipital instability, Leukemia, Immunodeficiency, Duodenal atresia, Alzheimer's disease, Thyroid dysfunction, Endocardial cushion defect.
5. Ovarian dysgenesis
6. Elevated estradiol to testosterone ratio
7. b,c,d

Chapter IV.4. Inborn Errors of Metabolism
Catherine Y.H. Wagoner, MD

This is a 2 day old male infant who is referred from an outside hospital for persistent hypotonia and mild respiratory distress since birth. He also has feeding intolerance characterized by emesis following each feeding. He is the product of a full term pregnancy to a 26 year old G1P1Ab0, O+, hepatitis B negative, rubella immune, STS negative mother via NSVD with Apgar scores of 7 and 8 at 1 minute and 5 minutes, respectively. Birth was complicated by a nuchal cord x 1 and a maternal fever to 102 degrees just prior to delivery for which one dose of ampicillin was given. After delivery, the infant required some blow-by oxygen and was transferred to the newborn nursery. In the newborn nursery, the infant continued to require oxygen until 2 hours of life when he was noted to have adequate oxygen saturations in room air. A CBC was done which was reported as unremarkable. The baby nursed overnight without any difficulty, and was able to pass his first meconium at less than 24 hours old. However, his first breastfeeding was followed by emesis. A second feeding of water also resulted in emesis. Due to the persistent hypotonia, feeding intolerance, and continued mild respiratory distress despite adequate oxygenation, the infant was transferred to a tertiary care neonatal intensive care unit (NICU).

Exam: VS T 36.5, P 136, RR 44, BP 58/41, oxygen saturation 100% in room air. Wt: 3.95 kg (80%ile). He is a term-appearing male infant who is noted to be slightly tachypneic and intermittently grunting. His head, ears, eyes, nose and oropharyngeal structures are without obvious abnormalities, except for his tongue which is remarkable for lateral fasciculations. His neck is supple. His lungs are clear, but he has notable intermittent grunting. His heart is regular with no murmurs. His abdomen is flat and soft, but his liver is palpable 2 cm below RCM. His extremities are normal, with 1+ pulses. His DTRs are absent. Genitalia are normal. He is hypotonic with poor head control.

A full sepsis workup is done and he is started on empiric antibiotics. An ABG demonstrates a severe metabolic acidosis with pH 7.22 and Bicarbonate 10. Anion gap is 23. Lactic acid and ammonia levels are elevated.

A bicarbonate infusion is initiated to treat the acidosis, dropping the base deficit from -13 to -5, and then to +6. After consultation with genetics, it is felt that the infant likely has a defect in energy metabolism based on the persistent hypotonia and severe acidosis. A metabolic defect workup is done, including urine for organic acids, plasma for amino acids, and muscle biopsy for fibroblast culture and electron microscopy analysis. He is started empirically on a vitamin cocktail consisting of thiamine, niacin, riboflavin, B12, biotin, and L-carnitine for the possibility of a fatty acid oxidation or mitochondrial defect. An MRI on day 3 of life reveals severe cerebral atrophy and developmental brain anomalies including agenesis of the corpus callosum. He later decompensates requiring life support. The severe metabolic acidosis recurs and additional sodium bicarbonate infusions are required. Despite this level of support, he does not improve. A decision is made by his parents and the medical team to withdraw support, since the infant's condition is felt to be terminal.

Inborn errors of metabolism (IEM) are a diverse group of disorders. They are genetically based defects of the normal biochemical processes of the body that are required to maintain homeostasis (1). The potential for a problem is great since there are a great number of biochemical reactions that must be enzymatically carried out for normal metabolism. An enzyme defect in any pathway (e.g., Krebs cycle, urea cycle, oxidative phosphorylation, etc.) will potentially result in a condition that is incompatible with life, unless a therapeutic way to circumvent the metabolic defect can be accomplished. Unfortunately, many and probably most of the diseases in this group can lead to a debilitating and even tragic ending, as illustrated in the case above. Due to the sheer number of disorders classified as inborn errors of metabolism, literally hundreds with more being discovered each year, it would be impossible to give a comprehensive review of the subject in a single book chapter. However, there are several overriding principles and practices that are fundamental to the diagnosis and management of the patient with a suspected inborn error of metabolism.

The objectives of this chapter will be to: 1) Understand the basic genetic mechanisms which underlie inborn errors of metabolism. 2) Know some of the more commonly affected biochemical pathways that manifest as metabolic disease. 3) Learn to recognize the subtle signs and some of the constellations of symptoms that may point toward a specific metabolic disease. 4) To learn about the Hawaii State Newborn Screening Program, its goals, and the systems in place to ensure the identification of babies who may have a correctable or treatable disorder.

Some of the great discoveries of science in the 20th century were the identification of biochemical pathways in the body that facilitate the existence of life in all organisms. These biochemical processes, such as the Krebs cycle that converts glucose to energy in the form of ATP and the urea cycle that converts ingested nitrogens into a form that can be excreted, form the basis for the routine production of energy from food, excretion of waste products, and the regulation of the internal environment of the body.

There are literally hundreds of individual steps in the body's processes. Roche Pharmaceuticals Group has an interactive diagram of most of the known biochemical processes on their website (2). It is these biochemical steps that are the sites of defects that result in metabolic disease. Since each step is dependent on the product of the previous step to provide the substrate for a reaction, a "mistake" in either the substrate produced or the enzyme required for the reaction will result in a seriously magnified effect on all the products of the

reactions downstream from the defective step. Ultimately, this may result in the inability to produce a necessary end product or to carry out a detoxification process.

The extent to which a metabolic defect may affect the function of the body is highly dependent on the final product of a biochemical cascade. For example, in ornithine transcarbamylase deficiency (OTC), a part of the urea cycle, carbamyl phosphate and ornithine are converted to citrulline. Citrulline is able to move outside the mitochondria, thereby transporting waste products of respiration to the cytoplasm where they can be processed further and ultimately excreted from the body. In OTC deficiency, there is accumulation of the upstream products of the reaction that leads to hyperammonemia. Over time, the high levels of ammonia will affect the brain, due to the toxicity of the waste product on the neurons. This will lead to the ataxia, seizures, cerebral atrophy, and encephalopathy observed in this disease (1-12).

It is of primary importance to understand the variable genetic mechanisms that can cause abnormal biochemical functioning. DNA is transcribed into ribonucleic acid (RNA) that is then processed into messenger RNA, which is then transcribed to a protein that may undergo further processing to become a functional enzyme, carbohydrate, signaling protein, hormone or structural element. Within this whole process of DNA to protein, there are multiple regulatory processes and feedback loops that will alter the rate of the transcription of DNA, processing of RNA, and the production of the final product. Thus, any defect in the DNA will lead to a change in the whole cascade and ultimately may affect multiple systems and biochemical processes.

One might postulate that a metabolic defect would render an individual unable to survive without modern medical interventions (e.g., transplantation, life support machines, exclusionary diets with special supplemental formulas). In fact, that is very likely true. Many infants who died in early childhood prior to the advent of sensitive diagnostic testing may have succumbed to a potentially treatable metabolic disease. It is easy to see that there is a natural selection against individuals with metabolic diseases, especially those who have a decrease in survival or basic life functioning.

It is, therefore, not surprising that many of the metabolic diseases are inherited in an autosomal recessive, X-linked recessive (males only), or sporadic (new mutation) pattern (1). Conditions that are lethal prior to reproductive age would not survive in the gene pool unless the condition was recessive (the heterozygous state could survive in the gene pool). Thus ALL lethal conditions are recessive or spontaneous new lethal mutations. In urea cycle defects, every known deficiency is autosomal recessive except OTC deficiency which is X-linked recessive (1). This also holds true for the lipidoses (disorders in lipid metabolism leading to the accumulation of lipoid material within cells). Niemann-Pick, Gaucher, Krabbe, and metachromatic leukodystrophy are all autosomal recessive, if a case is not sporadic (3). The other causes of neonatal degenerative encephalopathies, such as peroxisomal disorders and mitochondrial disorders are also autosomal recessive or X-linked recessive (4).

How might one go about determining whether an infant has a metabolic disease? The answer will always be clinical suspicion. There are a few "classic" presentations that should trigger consideration of an inborn error of metabolism as a reasonable possibility. These include metabolic acidosis, hyperammonemia, hypoglycemia and unusual odors. The respective clinical manifestations of these abnormalities are described below.

In urea cycle defects, the common toxin is ammonia (NH3), since the urea cycle is designed to excrete excess nitrogen. Therefore, the presentation of this group of defects is quite similar. Hyperammonemia causes an encephalopathic picture. Presenting signs and symptoms include vomiting, lethargy, poor activity, poor feeding, decreased mental status, and even coma. They may eventually develop spasticity, mental retardation, seizures, and ataxia. These disorders usually present in the first few days to weeks of life as the ammonia waste product accumulates quickly, leading to serum ammonia levels which are described as "sky-high" (>1000 umol/L). The afflicted newborn very rapidly decompensates (1,4). The initial clinical presenting signs and symptoms (other than hyperammonemia) more commonly signal a serious infection of the newborn. It is very difficult to differentiate the two disease processes. However, the existence of these symptoms along with low risk for a neonatal infection may raise the index of suspicion that would lead the clinician to conduct a thorough laboratory evaluation for a metabolic condition along with the sepsis workup.

A group of metabolic disorders related to the urea cycle defects is the organic acidemias. These are caused by defective processing of the amino acids resulting in accumulation of organic acid byproducts or lack of production of a necessary end product. The symptoms are very similar to the urea cycle defects; however, there are subtle laboratory differences. While urea cycle disorders result in hyperammonemia without acidosis and only occasionally hypoglycemia, the organic acidemias (as the name suggests) result in metabolic acidosis and hyperammonemia that is more on the order of 200-900 umol/L. One of the best understood diseases from this class of metabolic diseases is Maple Syrup Urine Disease (MSUD).

MSUD occurs in the immediate neonatal period, presenting with acute decompensation within the first 2 weeks of life. Symptoms include lethargy, poor feeding, vomiting, and seizures, which eventually lead to coma and cerebral edema. Laboratory evaluation yields hypoglycemia, hyperammonemia (to a lesser degree than in urea cycle defects), acidosis, and ketosis. The urine from these patients has a striking odor of maple syrup.

Phenylketonuria (PKU), one of the best understood genetic disorders and the first to be screened for in Hawaii (1966) (5), results from phenylalanine hydroxylase (PAH) deficiency. The enzyme deficiency leads to build-up of phenylalanine that is toxic in high levels to brain growth and nerve myelination. This causes mental retardation, abnormal behaviors and skin rashes. In addition, the PAH enzyme is necessary to convert phenylalanine to tyrosine which is required for melanin synthesis. With a defective enzyme, the individual is unable to produce proper levels of tyrosine which results in poor pigmentation of skin and hair (1,5).

Galactosemia is one of the commonly occurring disorders of carbohydrate metabolism. This disease occurs from a deficiency of galactose-1-phosphate uridyltransferase with the deficiency most noticeable in those organs which utilize the most energy (liver, brain, kidney and adrenal gland). Over time, there is an accumulation of galactose-1-phosphate, which manifests as vomiting, lethargy, diarrhea, cataracts, developmental delay and mental retardation, liver and kidney disease. In galactosemia, there is an increased likelihood of sepsis from gram negative organisms that may cause death in the neonatal period (1,4,5).

In an infant who has signs and symptoms consistent with a metabolic disorder, there are certain diagnostic steps that can help delineate what type of metabolic disorder could exist. Of course, the most important evaluation is always the history and physical. With metabolic disorders, one must always ask if there is a family history of early infant death or disability, developmental delay, mental retardation, or seizures. There should also be an assessment of the likelihood that the presenting illness is sepsis, which is much more common than metabolic disorders (4). Thus, some investigation for neonatal infection risk factors should be conducted (e.g., maternal fever, prolonged rupture of membranes, maternal colonization with group B strep, intrapartum maternal antibiotic treatment, fever or temperature instability in the infant, the presence of respiratory distress, etc.).

When a reasonable suspicion of a metabolic disease is established, then an appropriate workup can be undertaken. Laboratory evaluation should include a full sepsis workup (CBC, blood culture, urine culture, chest x-ray, cerebrospinal fluid studies and culture),

since sepsis may not be easily distinguished from an inborn error of metabolism. In addition to the sepsis workup, metabolic screening laboratories should include a glucose level, electrolytes, an arterial blood gas, ammonia level, lactic acid level, urinary ketones, and liver function tests. Definitive diagnosis will depend on what type of metabolic disorder is suspected.

Once the screening laboratories are available, one can systematically eliminate possible diagnoses until there are only a few possibilities left. Then, a few specific diagnostic tests can be performed to hopefully, identify the type of metabolic disorder that is present.

The first useful marker is the ammonia level. Urea cycle defects have extremely elevated ammonia levels, sometimes in excess of 2000 ug/dL. Organic acidemias and benign transient hyperammonemia of the newborn (THAN) have ammonia elevations that can overlap, but are not usually as high as those found in urea cycle defects.

The next useful laboratory marker is the presence or absence of hypoglycemia. Infants with elevated ammonia levels in the presence of hypoglycemia have a reasonable likelihood of having an organic acidemia. Infants with hyperammonemia without hypoglycemia tend to have urea cycle defects. Hypoglycemia without hyperammonemia can signal a carbohydrate metabolism defect (e.g., galactosemia, defect in gluconeogenesis, or a glycogen storage disease) or a fatty acid oxidation deficiency in the older infant.

Metabolic acidosis is a key tool in the differentiation of urea cycle defects versus organic acidemias, but it is also quite useful in the evaluation of respiratory or energy transport chain defects. Persistent, severe, metabolic acidosis with absence of urine organic acids will signal primary lactic acidosis. The presence of primary lactic acidosis usually means a defect in pyruvate metabolism (leading to inability to convert lactic acid back to pyruvate to enter the Krebs cycle), gluconeogenesis disorder (leading the body to scavenge pyruvate which is converted to lactic acid with ATP production), respiratory chain defect (causing inability to produce ATP during the Krebs cycle), or a mitochondrial disorder (e.g., error in oxidative phosphorylation). If the metabolic acidosis is due to a primary lactic acidosis, a lactate/pyruvate ratio may be helpful to further narrow the differential diagnosis (4).

Although it may be possible to determine the general class of metabolic defect, it is often not possible to determine the exact enzyme which is defective or lacking. For example, since there are so many enzymes involved in oxidative phosphorylation, a defect of any one of these will result in a lethal condition.

Current diagnostic studies for inborn errors of metabolism have limitations. The primary drawback is the 3-4 day turnaround time from receipt of the sample to the results being available. A critically ill infant may not be able to survive that time period without appropriate treatment. Thus, in the first few days it is crucial to initiate empiric therapy. This should be done with the available clinical and laboratory evaluation in conjunction with a metabolic specialist guiding treatment.

The presence of a possible organic acid or urea cycle defect requires that the patient undergo protein restriction to prevent accumulation of toxic metabolites or hyperammonemia. However, this requires prevention of catabolism of body protein for conversion to energy (i.e., gluconeogenesis) to prevent additional nitrogen waste production. Thus, an infusion of proper carbohydrate calories should be initiated as soon as possible. In infants, this is usually 10% dextrose (a simple hexose) water intravenously at 80-100 ml/kg/day (1,4).

Many of the organic acidemias and urea cycle defects can be mitigated with the use of vitamins and cofactors that can bypass the defect by shunting the toxic metabolites to an alternate pathway or they can serve as transport molecules to shuttle byproducts in and out of the mitochondria. For example, in citrullinemia and argininosuccinic aciduria, infusions of arginine can result in significant drops in the ammonia level. Biotin can be used in carboxylase deficiencies while vitamin B12 can be useful in some forms of methylmalonic acidemias (1).

After 2-3 days, the body's natural processes will require amino acid input for normal functioning. Otherwise, catabolism and metabolic decompensation can occur. If a definitive diagnosis has not been established, there are commercially available protein-free formulas (e.g., Prophree by Ross) that can be used until a tailored diet can be established after the diagnosis is made (4).

Fatty acid oxidation disorders can present with hypoglycemia with lack of ketones present in the urine. Obviously, the hypoglycemia can easily be treated with a glucose infusion. The inability to process fatty acids means that these individuals will need their dietary fat restricted since they would not be able to metabolize fat. In addition, L-carnitine, a transport molecule in the liver, should be given as a supplement.

Galactosemia, which is suspected by the presence of reducing substances in the urine, is treated by elimination of galactose and lactose (glucose + galactose) from the diet. In infants, this can be accomplished by the exclusive use of soy formulas (no cow's milk or breast milk) (1,4).

Other therapy is strictly supportive: ventilatory support for those infant who are in imminent respiratory failure, bicarbonate infusions for infants with severe, unremitting acidosis, volume expansion for signs of hypoperfusion. Exchange transfusions or hemodialysis may be used in patients with high levels of ammonia. However, if empiric therapy and protein restriction are implemented early with the suspicion of a metabolic disorder, many infants may never have to undergo dialysis or exchange transfusion. Definitive therapy will depend on the metabolic defect that is identified.

The State of Hawaii has a newborn metabolic screening program which began in 1966 with PKU, but has since progressed to the inclusion of metabolic, endocrine, and hemoglobin disorders. The newest panel of disorders for which all newborns are screened includes congenital hypothyroidism, phenylketonuria, hemoglobinopathies, biotinidase deficiency, galactosemia, maple syrup urine disease, and congenital adrenal hyperplasia (5).

The Newborn Screening Program (NSP) in Hawaii has been enormously successful in capturing nearly all infants born in the State of Hawaii. Newborn Screening Programs exist in all 50 of the United States. Each state has jurisdiction over what panel of screening tests exists and the timing of the blood collection (http://www.aap.org/policy/01565t1.htm). For example, in Hawaii, the blood collection is conducted during the newborn period, prior to discharge from the hospital. Even in the Neonatal Intensive Care setting, the blood collection is done in the newborn period, but may be done earlier if the neonate is going to receive a blood transfusion.

Almost all results are reported out to the primary care provider within 2 weeks of the testing. The abnormal results are flagged for the physician and instructions for diagnostic testing, either at the Regional Laboratory (Oregon for all tests from Hawaii) or at a laboratory of the physician's choice, are included. Most abnormal results are also mailed with an instructional pamphlet for the family and physician of the affected child describing the disorder and possible diagnostic, therapeutic, and reproductive considerations.

The NSP was designed as a key preventive public health tool to identify disorders that have a treatment that when started early, can lead to reductions in mental retardation, physical disability or death.

Questions

1. True/False: Infants with an inborn metabolic defect are always symptomatic within the first two weeks of life.

2. Many of the metabolic defects can present clinically like which of the following:
   a. sepsis.
   b. formula intolerance or gastroesophageal reflux.
   c. necrotizing enterocolitis.
   d. neonatal hepatitis with liver failure.
   e. all of the above.

3. Newborn screening is designed with which of the following principles in mind:
   a. To identify all infants with the metabolic diseases that are included in the screening panel.
   b. To generate more paperwork for the physician.
   c. To screen for diseases that have no cure, but that can be alleviated through early intervention.
   d. To ensure early screening of future offspring for the family of affected infants.
   e. To screen for all possible metabolic diseases.
   f. To disseminate information regarding genetic/metabolic disease to the public and the physicians.

4. True/False: None of the metabolic diseases have a cure.

5. An infant with hyperammonemia, metabolic acidosis, and hypoglycemia most likely has what class of defect:
   a. fatty acid oxidation disorder.
   b. galactosemia.
   c. organic acidemia.
   d. urea cycle defect.
   e. lipid storage disease.

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Answers to questions

1. False: Many infants with metabolic defects classified as storage disorders (lipid storage disorders) and fatty acid oxidation defects will present at many months of age.

2. e. And, there are many other disorders that can be on the list of possibilities, including child abuse (shaken baby).

3. c, d, f. The other answers are incorrect because: a. Newborn screening is not a diagnostic tool; it merely indicates need for further definitive testing. b. Obviously, physicians do not need more paperwork. e. Ideally, newborn screening could identify all metabolic disease, however, since cost and technology are prohibitive, the current principles are to screen for diseases which have a "significant" prevalence in a population and have some potential for treatment.

4. True: Unfortunately, there are no permanent cures, only lifelong supportive measures to mitigate the effects of the metabolic disease.

5. c

Chapter IV.5. Inherited Connective Tissue Disorders
Steven C. Crook, MD

A 3 year old male presents to the ER with a gross deformity of his left upper arm. His mother reports that her son "slipped while taking a bath" and struck his arm on the side of the tub. He has a history of a previous right femur fracture that resulted from a fall down the stairs one year ago. In addition to the gross deformity to the left humerus, his physical exam is notable for bluish sclera and no other signs of trauma (no bruising or scars). A skeletal survey is ordered by the ER physician, who thought that the injury did not fit the history provided by the parent. The plain films reveal a comminuted fracture in the middle of the left humerus, and signs of multiple healed rib fractures in addition to the healed right femur fracture. The ER physician notifies child protective services (CPS) as required by law. He is later referred to a geneticist who makes the diagnosis of osteogenesis imperfecta.

The true connective tissue disorders are not the acquired immunologic disorders of lupus, rheumatoid arthritis, or vasculitis, but are instead inherited disorders of the molecules which comprise the various connective tissues. While these diseases were originally defined by their most severe presentations, their modern definitions have been broadened to recognize a spectrum of disease from the most severe cases to near-normalcy. The clinician should focus on recognizing the potentially life threatening presentations of diseases and differentiating subtle presentations from more common diagnoses.

Osteogenesis imperfecta (OI) presents in a varied range of phenotypes which share a common molecular basis: a defect in type I collagen production. Type I collagen, the principal structural component of all bones, is composed of 3 procollagen proteins: 2 copies of the gene product of COL1A1, and 1 copy of the gene product of COL1A2. Eighty to ninety percent of individuals diagnosed with OI have mutations in one of these two genes, but the number of different mutations in each of these genes is so great that DNA testing is not feasible. Molecular confirmation of an OI diagnosis is achieved through culturing dermal fibroblasts, isolating and amplifying the genes and gene products of COL1A1 and COL1A2, and assessing the quantity and quality of these procollagen proteins. The classic clinical description of OI is a combination of fragile bones, blue sclera, and deafness. Sillence described four distinct types of OI. More recently however, we have learned that the clinical variability of OI is so great as to render these distinctions solely of academic importance.

In its most severe form, OI is incompatible with life. Affected infants are either stillborn or die in the early neonatal period as a result of extreme skeletal fragility. These patients produce a normal quantity of structurally defective collagen. In its mildest form, OI causes bones to be more brittle than normal, resulting in a propensity for fractures to occur or it may go undiagnosed entirely. These patients do not produce malformed collagen; instead they produce less than normal quantities of normal collagen. Life span may be affected in the extreme, or not at all. Hearing loss may be present at birth, develop in childhood, or may never occur. The color of the sclera ranges from a striking dark blue to normal white. Predicting prognosis in early life is very difficult and is best achieved by sorting the patient into one of the four Sillense groups upon which most research is based. Rough prognosis for future ability to walk is based on the ability to sit independently by 10 months of age. OI does not affect cognitive ability.

Treatment always includes physical therapy and often includes orthopedic intervention. The critical goal is achieving greater than 3/5 muscle strength in the proximal muscle groups of the extremities. Fine motor skills are usually unaffected by OI. Bowing of long bones is very common and if the curvature is greater than 40 degrees, prophylactic intramedullary rodding is often performed. A careful fracture history is important to target weak bones in an individual and specifically strengthen the muscles around those bones. Growth failure is quite common but incompletely understood. While no medical therapy is currently available, there are several theoretical gene therapy interventions. As the most severe form of OI is caused by incorrectly formed type I collagen, the use of antisense RNA or ribosomal RNA to prevent the translation of mutant collagen would convert a severe form of OI into a less severe one. Other researchers are working on bone marrow transplant of cells that produce normal collagen in order to increase the amount of type I collagen available for bone construction.

As the case illustrates, the recognition of OI is crucial to differentiating abuse from accidental or pathological trauma. The prevalence of OI recognizable at birth is 1 in 20,000. The actual prevalence of all OI including the mildest and least often diagnosed forms is unknown, but the disorders certainly remain quite rare. For comparison, there are an estimated 30,000-50,000 children with fractures caused by abuse each year, and approximately 200 children born each year with OI. In general, the radiographic findings of abused children include epiphyseal and metaphyseal fractures of the long bones. In contrast, OI fractures usually occur in the shaft of long bones with relative sparing of the metaphysis. Rib fractures occur in both; however, it is the consensus of radiologists and clinicians that in the vast majority of cases these two causes of fracture can be differentiated. If doubt persists, a geneticist should be consulted to determine if biochemical analysis of dermal fibroblasts would be useful.

In general, the severe forms of OI which result in infant death, are inherited in a recessive manner since this is the only way that such a mutation would be able to remain in the gene pool. The more occult forms of OI are usually inherited in an autosomal dominant pattern, which means that the family history should be positive. A family history which is positive for family members who have frequent fractures (especially those which occurred with minor trauma), scoliosis or other orthopedic conditions, should strongly raise the suspicion of OI. Family history is not totally reliable since there is variability in the expression of the condition and there are many spontaneous mutations.

Marfan syndrome is a spectrum of abnormalities involving the skeleton, great vessels, and eyes resulting from defects in a single gene responsible for a component of elastin. Fibrillin 1 is the protein produced from the gene FBN1 which is found mutated in nearly all cases of Marfan syndrome. The protein is used to create microfibrils which form elastin and are also used to anchor some tissues (e.g., suspensory ligament of the lens). Marfan syndrome is autosomal dominant and hundreds of defects have been found in the FBN1 gene; all of which create defective fibrillin proteins in normal quantities. The diagnosis is based on a clinical constellation. Four of the following major criteria must be present: pectus carinatum (pigeon breast), pectus excavatum (concave sternum) sufficiently severe to require surgery, reduced upper to lower segment ratio (measurements of pubis to top of head and pubis to soles, respectively), positive wrist and thumb signs (thumb protrudes beyond 5th finger when a closed fist is made), scoliosis greater than 20 degrees of curvature, reduced extension of elbows, medial displacement of medial malleolus causing pes planus (flat foot or collapsed longitudinal arch), or protrusio acetabuli (inward bulging of the acetabulum into the pelvis). If a family member has been diagnosed with Marfan syndrome, then the presence of a single major criteria along with several of the following minor criteria is sufficient: pectus excavatum (not requiring surgery), joint hypermobility, high arched palate, or typical facial appearance. There is no mental retardation or negative impact on cognitive development.

Life expectancy is reduced in Marfan syndrome. This is commonly due to progressive dilation of the aortic root and an increased risk of aortic dissection with advancing age. Death often occurs in the third decade in the absence of palliative surgery to prevent aortic valvular regurgitation and aortic rupture. Considerable debate remains among the surgical community as to the proper timing of prophylactic aortic arch repair. Currently, an aortic diameter of 50 mm along with cardiac symptoms is a conservative guideline, as death is common with root enlargement beyond 50 mm.

As with all of the heritable disorders of connective tissue, Marfan syndrome presents along a spectrum of severity. It is crucial to consider this diagnosis in patients with long thin limbs, joint laxity, or vision problems because the potentially lethal cardiac complications of the disease can be prevented. However, it is important to note that many patients with Marfan syndrome do not have the typical Marfanoid appearance. Likewise, it is important to keep in mind that patients in their twenties and younger can present with aortic root dilation causing aortic regurgitation, aortic dissection and aneurysm. When the diagnosis is suspected, an echocardiogram (to measure aortic root size) and a slit lamp examination (looking for ectopia lentis, an upward dislocation of the lens, is present in 50-80% of cases) should be performed.

Ehlers-Danlos is a group of inherited defects involved in the production of collagen fibers. The result is a wide clinical spectrum of diseases which share hyperextensible doughy skin (often described as having a velvety soft texture), atrophic scars, joint hypermobility, connective tissue fragility, and bruising. The defect can occur at any step in the production of collagen fibers. The procollagen fiber itself can be defective, as can enzymes which perform the post-translational hydroxylation of lysine or any of the enzymes which chaperone (i.e., molecular regulation) the assembly of procollagen fibers into normal collagen. Several different genes have been identified but many cases remain without molecular description. The disease occurs in up to 1/5000 live births, making this the most common of the connective tissue disorders. Clinical presentation usually occurs after birth. Many distinct phenotypes have been described, but as with the other connective tissue disorders, the majority of affected individuals do not fit into these groupings.

Skin fragility is caused by a thin dermis depleted of collagen fibrils. Splits or tears over bony prominences are common. Minor trauma cause widely gaping wounds which heal slowly. Surgery is complicated by frequent wound dehiscence. Patients will often present to ERs with a history of multiple lacerations requiring suture closure despite relatively minor trauma. Vascular fragility may be due to defects in collagen type 3, resulting in vessels with low tensile strength. In these individuals, aneurysms, arteriovenous malformations, and dissections are common. Ecchymoses are present with hemosiderin deposits over bony prominences. Hyperextensibility and joint hypermobility are caused by ligamentous laxity (which predisposes to dislocated hips in infants). Clubfoot, joint effusions, and spondylolisthesis (vertebral displacement) may also be present. The gastrointestinal tract can be similarly affected; decrease in tensile strength of the bowel walls predisposes to spontaneous rupture. Bony involvement usually manifests as kyphosis. Individuals diagnosed with E-D usually display one or a combination of these different symptoms. Life expectancy is highly variable in Ehlers-Danlos. The most severe complications of disease result from bowel and vasculature weakness. Hypermobility syndromes represent the mild end of the spectrum described by the Ehlers-Danlos disorders. No curative therapy is available. Vitamin C helps some individuals who are deficient in lysyl hydroxylase (which uses vitamin C as a cofactor in strengthening collagen fibers).

Other Connective Tissue disorders: Homocystinuria is an inborn error of methionine metabolism which results in a Marfan-like syndrome. The two disorders are differentiated by the presence of mental retardation in homocystinuria. Stickler syndrome is a constellation of progressive myopia, sensorineural hearing loss and hypomobility associated with distinct facial features. The diagnosis is suspected in neonates with swollen wrists, ankles or knees, and in children with hearing loss and marfanoid characteristics.

Questions

1. How is osteogenesis imperfecta differentiated from child abuse?
2. How are future fractures prevented in children with OI?
3. Name 3 major criteria for Marfan syndrome
4. What is the most common cause of early death in children with Marfan syndrome?
5. What are 3 of the cardinal features of Ehlers-Danlos?
6. How is homocystinuria differentiated from Marfan syndrome clinically?

Related x-rays

Occult osteogenesis imperfecta case: Yamamoto LG. Fussiness Following Minor Trauma in an Infant. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1999, volume 6, case 2. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v6c02.html

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Aortic dissection case: Feng AK. Severe Acute Chest Pain in an Adolescent. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1995, volume 3, case 12. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v3c12.html

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Answers to questions

1. Presence of associated physical findings. Family history. Location of fracture (femur and radius vs tibia and radius), type of fracture (comminuted mid shaft vs epiphyseal and greenstick). Radiographic appearance of the fractures (i.e., presence of osteopenia).
2. Careful fracture history, identifying weak bones, and targeting physical therapy to strengthen those bones.

3. Any of the following: pectus carinatum (or excavatum sufficiently severe to require surgery), reduced upper to lower segment ratio, positive wrist and thumb signs, scoliosis greater than 20 degrees of curvature, reduced extension of elbows, medial displacement of medial malleolus causing pes planus, protrusio acetabuli.

4. Aortic root dilation causing aneurysm and dissection.

5. Any three of the following: hyperextensible doughy skin, atrophic scars, joint hypermobility, connective tissue fragility, and bruising.

6. Marfan syndrome, unlike homocystinuria, is not associated with mental retardation.

Chapter IV.6. Genetic Testing and Gene Therapy
Steven C. Crook, MD

Your nurse knocks on the door interrupting your examination of a child. On the phone is a lab technician from another state who reports that a newborn screen reveals a positive test for galactosemia in one of your patients. The patient, you recall, is the first child of a young professional couple. Reviewing her chart you are reminded that there were no perinatal complications. The child was discharged home from the hospital at just under 48 hours of age, he appeared well with only a 3% weight loss and mild facial jaundice upon follow-up at day 4 of life. His parents reported no breast feeding difficulties and, despite their concern for the number of hours their new baby slept, the new family appeared to be thriving.

Genetic testing has received much attention in the press, with interest focusing on the ethics and repercussions of genetic information. Despite this attention, most people do not realize that for the past twenty years, almost all newborns in the United States have been screened for a number of genetic diseases. Almost all newborn screen tests are quantitative tests for the presence or absence of metabolic or endocrine molecules. When the concentration of the tested molecule is greater or less than a level determined by the reference lab, the test is reported as positive. In order to provide 100% sensitivity for disease, the level of positive detection must be adjusted to a point at which specificity may be quite poor. Classical galactosemia affects roughly 1:59,000 infants born in the US. In 1994, 10,210 infants tested positive on newborn screening for galactosemia. Of these, 54 infants were confirmed to have the disease (positive predictive value 0.53%). Improvements in mass spectroscopy are greatly increasing the number of inborn errors of metabolism that can be efficiently screened in all newborn infants.

Metabolic screening represents one type of genetic testing. For diseases such as sickle cell disease and cystic fibrosis, in which the disease gene and disease alleles are known, very specific tests based on DNA are used. Unlike the quantitative screens for inborn errors, DNA-based tests have virtually 100% specificity. These tests provide binary answers (yes/no) to the hypothesis "does this particular unique region of DNA exist in this patient?" With this knowledge, we can understand the current limitations of DNA-based genetic testing.

1. A single gene must be discovered and sequenced, which when altered, produces a recognizable disease state.
2. The various disease-sequence alterations must be catalogued.
3. For every detectable alteration, a single unique test must be created and performed.

Since sickle cell disease is caused by a single diseased allele in all patients affected, a single PCR (polymerase chain reaction) test can diagnose it with near perfect sensitivity and specificity. On the other hand, some diseases such as Duchenne muscular dystrophy or osteogenesis imperfecta, may result from one of hundreds of different possible alleles. In these cases, DNA-based testing is not practical. Cystic fibrosis represents a middle ground, in which hundreds of disease alleles exist, but only a handful produce the vast majority of illness in select populations. In European descendants, the delta F508 allele represents 70% of disease alleles in that gene pool and four additional alleles represent another 10-20%. For this population, a handful of PCR based tests can be performed on a patient's blood which that cover the vast majority of possible alleles.

As more disease alleles are discovered, more tests can be run to determine if each allele is present in a given patient. Currently, most tests are PCR-based and involve duplicating small parts of a patient's genome in sufficient quantities to be detected on a gel by fluoroscopy or radioactivity. In the late 1990s, DNA chip technology was invented with the power to perform hundreds of thousands of DNA-based experiments simultaneously on a single patient. A DNA chip is a grid of hundreds to hundreds of thousands of individual matching tests mass produced on silicon wafers the size of a dime. Each matching test involves a small unique section of single stranded nucleic acid which is glued to the wafer in a specific grid position. A patient's DNA or RNA is extracted from blood, broken up into short strands, made single stranded (in the case of DNA) and then used to bathe the DNA chip. Sections of patient DNA or RNA which closely match specific test sequences on the chip bind and are detected. This technology has the potential to increase the sensitivity of DNA-based genetic testing as disease alleles continue to be discovered.

There are several other methods to detect genetic based illnesses, including the visual inspection of chromosomes, the augmented inspection of chromosomes using fluorescent antibodies, and multiple methods of detecting the presence, absence and relative quantity of proteins.

A person's DNA essentially remains unaltered from the moment his/her mother's ovum and father's sperm join, until the day that the last nucleus in his/her body is destroyed. In theory, the information to predict susceptibility to all genetically based disease is available in zygotes and ancient human remains. As science progresses and discovers how genetic information predicts disease states, the ethical debates over how best to use the information must also progress. Currently, the AAP recommends:

1) The introduction of new newborn screening tests only if identification provides clear benefit to the child, the diagnosis can be confirmed after a positive screening test result, and treatment and follow-up are available for each infant tested.

2) Informed parental consent.

3) No screening of healthy children for the detection of disease-carriers (children with potential to pass on an inherited disease to their children) except in the case of certain prenatal screening tests in well informed teens.

4) No testing for adult onset illness until the child is an adult and is able to make informed decisions for him/herself.

Since the discovery that genetic information can predict disease states, people have been afraid that this information might be used in a discriminatory manner. One such fear is the possibility that insurance companies might use genetic test results to increase rates or even deny coverage to individuals with genetic susceptibility to expensive illnesses. So far, these fears are only speculative. A panel of lawyers, genetic counselors, and geneticists reported (at the 1999 meeting of the American Society of Human Genetics) that they had been unable to identify any cases of discrimination by health insurers (6).

Simply stated, gene therapy is medicine practiced with a nucleic acid based pharmacy. The patient is given nucleic acids in order to modify a pathologic pattern of protein expression. One form of gene therapy, bone marrow transplant, is currently in widespread use. The treatment for refractory leukemia involves massive chemotherapy to destroy all cancerous cells that are then replaced by a population of cells with "normal" cell cycle regulation. The more classical definition of gene therapy requires the modification of protein expression in existing cells. Only a handful of individuals have undergone this experimental form of therapy. These therapies are based on the idea of utilizing a virus as a vector to implant new genetic information into a patient's cells. Thousands of viruses have evolved to efficiently insert their DNA or RNA into specific human cell lines for the purpose of turning the cells into viral copy machines. In creating vectors, scientists remodel viruses, retaining the machinery to identify and infect specific cells (adenoviruses which preferentially affect respiratory epithelium, lentiviruses which preferentially attach to T-cells, and herpes viruses which recognize neurons) but change the genetic material which the virus inserts into the cells.

The inserted nucleic acid can take any of the following forms: 1) RNA can be used to immediately translate functional proteins. 2) RNA or DNA can be engineered to be the non-coding ("anti-sense") sequence of a specific pathologic mRNA so as to produce functionless double stranded mRNA. 3) Ribozymes (RNA with the enzymatic ability to degrade specific mRNAs) can be introduced to degrade pathologic mRNA. 4) DNA can be inserted in the middle of a disease gene to turn off pathologic production. 5) Sections of DNA can be inserted permanently into the target cell to restore the production of proteins, or alter the degree to which proteins are expressed by the cell. Despite the elegance of these theories, no disease state has been "cured" using gene therapy in a human patient as of this writing. The failure of gene therapy to date, is attributable to both vector and nucleic acid design, which are limited by our rudimentary knowledge of basic cell and molecular biology.

The dream of the Human Genome Project, that one day patients will provide a drop of blood, a scraping of cheek cells, or a hair follicle and be provided with a set of probabilities of acquiring all disease states and a range of treatment options based on targeted gene therapy, is far from being realized. However, in the early 1990s the Human Genome Project's basic goal of sequencing the entire genome also appeared a pipe dream which was projected to run over time and budget. In 2000, five years ahead of projections, the first working draft sequence of a human genome was completed. Noninvasive, perfect tests will never become available for all diseases and silver bullets filled with DNA will not rid the world of illness, but it is certain that the power of nucleic acids to diagnose, treat, and prevent illness will become significantly greater in the coming decades.

Questions

1. True/False: Current newborn screening can diagnose a handful of inborn errors of metabolism like Galactosemia?
2. What are the limitations of DNA based genetic testing?
3. Why is it not currently ethical to test a 7 year old girl for the BRCA1 (breast cancer 1 gene) mutations even if early breast cancer runs in her family?
4. Currently, what is the most widely used form of gene therapy?
5. What is the function of a gene therapy vector?
6. Describe the various methods of introducing nucleic acids into a cell to alter disease states.

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Answers to questions

1. False. Newborn screening is not diagnostic. Rather, it is a screen for illness with VERY poor specificity, which, if positive, must be followed with a more specific diagnostic test.
2. Sequence knowledge of the disease locus and mutant alleles and the 1:1 correlation of test to disease allele. For disease conditions with multiple mutant alleles, all possibilities must be specifically tested.
3. The disease does not affect the patient until adulthood when she can make her own decisions. There is no effective prophylactic treatment for a child that will prevent the illness before she reaches adulthood. Testing may be appropriate for a 17 year old who desires pregnancy, has the consent of her parents, and who plans to make the decision to become pregnant based on the information of the test.
4. Bone marrow transplant.
5. Vectors transport engineered nucleic acids (DNA or RNA) into existing human cells.
6. 1) DNA based: Insertion of intact functional gene. Insertion of intact functional promotor or exons to correct production. Insertion of DNA for the purposes of disrupting expression of a gene. Insertion of single stranded DNA for the purposes of binding to mRNA and preventing translation. 2) RNA based: Insertion of RNA to be reverse transcribed and incorporated into DNA. Insertion of RNA to be translated immediately. Insertion of RNA ribozyme to destroy mRNA. Insertion of anti-sense RNA to prevent translation of mRNA.

Chapter IV.7. Basic Genetic Principles
Bryan O. King, MS

Dr. G, the pediatric chief resident, rushes to the delivery room to assist with a resuscitation being attended by a first year resident and a medical student. The newborn has low Apgar scores and is not breathing well. Endotracheal intubation and ventilation results in improvement. The newborn is transferred to the NICU. A chest X-ray demonstrates severe demineralization of all the bones and multiple rib fractures. A skeletal survey demonstrates severe osteopenia and multiple fractures with crumpling of the long bones. Osteogenesis imperfecta (OI) is diagnosed. This infant dies at about one month of age due to respiratory failure. There is no family history of previous neonatal deaths or bone problems.

On the pediatric floor, there is a teenager with "osteogenesis imperfecta" who has sustained a tibia fracture. The father, aunt and two uncles of this patient also have OI. The house staff and medical students ask Dr. G to explain why one case of OI can be so severe, while another case can be relatively mild. Also, why does one case have a negative family history, while the other case has a positive family history? A second year resident mentions that this is similar to muscular dystrophy in which some cases are very severe (with no family history) and other cases are milder with a teen or adult onset (and sometimes with a positive family history).

A significant proportion of human illnesses have a genetic basis. The topic of genetic diseases is therefore broad and encompasses both inherited diseases as well as somatic diseases caused by spontaneous mutations. This chapter covers the mechanisms of gene and chromosome mutation and their relevance to both inherited and somatic diseases. Mendelian genetics and chromosome disorders associated with a variety of clinical conditions will also be reviewed.

Genetic mutations occur anytime there is a permanent change in the primary nucleotide DNA sequence. Mutations can be lethal, deleterious, or confer an evolutionary advantage. Genes and chromosomes can mutate in either somatic or germinal tissue. Somatic mutations can occur during embryogenesis or in dividing somatic tissue. A single somatic cell that mutates will be the progenitor for a clonal population of cells known as the mutant sector. This "patch" of developing mutant cells tends to stay close together and is phenotypically distinct from the surrounding population of normal somatic cells. If the mutation is compatible with cell survival, phenotypic variations can be visualized such as the pigmented lesions seen in McCune-Albright Syndrome. Somatic mutations are often associated with cancer because they can offer growth advantages. Cancer mutations occur in a special category of genes called proto-oncogenes, many of which regulate cell division. When mutated, such cells enter a state of uncontrolled division, forming a cluster of cells known as a tumor.

A germinal mutation occurs in germ cells which are specialized tissue that is set aside during development to form sex cells. If a mutant sex cell participates in fertilization, then the mutation will be passed on to the next generation. It is possible for mosaic germline mutations to occur in which case the mutation can be transmitted to some progeny but not others. This causes confusion when attempting to determine patterns of inheritance.

Mutations may be classified into three categories: genome, chromosome, and gene. Genome mutations involve the loss or gain of whole chromosomes, giving rise to monosomy or trisomy. These mutations are infrequently transmitted to the next generation because they are often incompatible with survival or at least result in reduced fertility. Thus, most monosomies and trisomies are the result of spontaneous events (new mutations). Chromosome mutations result from rearrangement of genetic material and result in structural changes to the chromosome (e.g., translocations, which will be discussed later). The most common type of mutations associated with hereditary diseases are gene mutations, the mechanisms of which will be briefly reviewed here.

Point mutations (single base substitutions) within coding sequences may alter the DNA in such a way that the new mutated sequence encodes a different amino acid. Because these mutations alter the meaning of the genetic code, they are called missense mutations. Sickle cell anemia is a classic example of a coding sequence point mutation which affects the beta-globin chain of hemoglobin. The nucleotide triplet CTC, which codes for glutamic acid, is changed to CAC, which codes for valine. This single amino acid substitution causes the formation of structurally abnormal hemoglobin resulting in a clinically significant hemoglobinopathy.

Point mutations can also change amino acid coding sequences into chain terminating stop sequences. Because these new stop sequences do not code for amino acids, they are known as nonsense mutations. An example of this occurrence again involves the beta-globin gene in a severe form of anemia known as beta-thalassemia. In this condition a point mutation affecting the codon for glutamine (CAG) creates a stop codon (UAG) leading to premature termination of beta-globin chain translation.

Mutations within noncoding sequences can also interfere with protein synthesis at various levels. Point mutations or deletions affecting promoter and enhancer sequences may suppress gene transcription. Such is the case in certain forms of hereditary hemolytic anemias. Lastly, deletions and insertions can cause frame-shift mutations unless the number of base pairs involved is three or a multiple of three.

All Mendelian disorders are the result of expressed mutations in single genes with a noticeable phenotypic effect. The number of these disorders is great with some estimates listing more than 5000 disorders. As the name implies, most of these conditions follow classic Mendelian patterns of inheritance. Although gene expression is usually described as dominant or recessive, in some cases, both of the alleles of a gene pair may be fully expressed in the heterozygote, a phenomenon known as codominance. Histocompatibility and blood group antigens are good examples of condominant inheritance.

In autosomal dominant (AD) disorders, if an affected heterozygous person marries an unaffected person, every child they have, carries a 50% chance of having the disease. AD disorders are generally compatible with survival until reproductive age since this is the only way that the mutation would be able to remain in the gene pool (i.e., if the condition were not compatible with reproduction, then the mutation would not be passed on). AD disorders are manifested in the heterozygous state so that at least one parent of an index case is usually affected (along with aunts/uncles on the affected parent's side of the family). However, every AD disorder has cases where neither parent is affected. In these cases, the disease is caused by new mutations of the egg or sperm. Also, the clinical features of a particular AD disorders can vary. For instance, some individuals inherit the mutant gene but are phenotypically normal. This is referred to as reduced penetrance, a termed that is expressed mathematically as the percentage of patients that phenotypically express their genotypic mutations. On the other hand, variable expressivity occurs when a trait is seen in all individuals carrying a mutant gene, but is expressed differently.

Autosomal dominant disorders usually do not involve diseases where there is a loss of function of an enzyme (i.e., enzyme deficiency states are almost never autosomal dominant). Because a 50% reduction of most enzymes can be compensated by the 50% that remain viable (i.e., the person is phenotypically normal), heterozygous enzyme mutations usually do not present with an autosomal

dominant pattern of inheritance. Instead, autosomal dominant disorders usually affect non-enzyme proteins that can be divided into two categories.

The first involves proteins that are involved in the regulation of complex metabolic pathways that are subject to feedback inhibition (e.g., regulator genes). For example, patients with familial hypercholesterolemia carry a loss of function mutation in the gene encoding the LDL receptor. As a result, there is a loss of feedback control of plasma cholesterol levels due to the fact that the liver is less capable of clearing circulating plasma LDL. Additionally, a reduction of LDL receptors on the liver reduces LDL entry into the liver which disrupts the negative feedback regulation of hepatic cholesterol synthesis. As a consequence of these receptor abnormalities, cholesterol levels are elevated and induce premature atherosclerosis resulting in increased risk of heart disease.

The second type of non-enzyme proteins that are affected by autosomal dominant disorders are certain structural proteins. The detrimental effects of reducing levels of a structural protein by 50% become clearer when considering that the abnormal products from a mutant allele can interfere with the assembly of a functionally normal multimeric complex. For example, the collagen molecule is a trimer in which the three collagen chains are arranged in a helical configuration. Each of the three collagen chains in the helix must be normal in order to produce a stable collagen molecule. Even a single mutant collagen chain disrupts the integrity of the trimeric complex. The effects of these autosomal dominant structural protein disorders are seen in conditions such as osteogenesis imperfecta (occult types), Marfan syndrome, and Ehlers-Danlos syndrome. A simplistic way of looking at this is to consider structural protein mutations like a wall of bricks composed of 50% normal bricks and 50% defective bricks (from the abnormal allele). Such a wall is likely to be very weak and eventually collapse.

Disease states with an autosomal recessive inheritance pattern comprise the largest category of Mendelian disorders. Most of these disorders are enzyme or protein factor deficiency states (e.g., hexose amidase deficiency, factor 10 deficiency). Because autosomal recessive disorders require that both parents have the mutant allele, such disorders are characterized by the following features: 1) the trait does not usually affect the parents, but siblings may show the disease, and 2) siblings have one chance in four of being affected with a recurrence risk of 25% for each subsequent birth.

In contrast to autosomal dominant disorders, the following features generally apply to autosomal recessive disorders: 1) The expression of the defect tends to be more uniform than in autosomal dominant disorders. 2) Complete penetrance is common. 3) Onset is frequently early in life. 4) Many autosomal recessive conditions result in defective non-functional enzymes (i.e., loss of enzyme function). 5) Autosomal recessive disorders include almost all inborn errors of metabolism. 6) Many of these disorders are incompatible with life.

All sex-linked disorders are X-linked, and most are X-linked recessive. There are no Y-linked diseases because the only functional gene on the Y chromosome is the determinant for testes. If this gene is mutated, then the person is infertile and hence, no inheritance is possible. In terms of X-linked recessive inheritance, the heterozygous female usually does not express the full phenotypic change because of the normal paired allele on the other X chromosome. However, because of random inactivation of one of the X chromosomes in females (a phenomenon known as Lyonization), there is a remote possibility for the normal allele to be inactivated in most cells, thereby permitting full phenotypic expression. (e.g., G6PD deficiency). An enzyme deficiency such as RBC G6PD deficiency is compatible with a relatively normal life span. Therefore, an affected male may pass on the abnormal X allele to his daughter, who may also receive an abnormal X allele from her unaffected heterozygous mother. Thus, this is another mechanism that a female could be affected by an X-linked recessive disorder. This is not possible if the affected condition is incompatible with survival to reproductive age.

There are only a few X-linked dominant conditions. They are caused by dominant disease alleles on the X chromosome. These disorders are transmitted by an affected heterozygous female to half her sons and half her daughters and by an affected male parent to all his daughters but none of his sons. Vitamin D-resistant rickets is an example of this type of inheritance.

The aberrations underlying chromosome disorders may take the form of an abnormal number of chromosomes or alterations in the structure of one or more chromosomes. In humans, the normal complement of chromosomes in a haploid cell is 23. A cell with any multiple of the haploid number is called euploid. Aneuploidy refers to conditions where errors occur during meiosis or mitosis that result in the formation of cells with a set of chromosomes that are not a haploid multiple. The most common causes of aneuploidy are nondisjunction and anaphase lag.

Nondisjunction occurs when homologous chromosomes fail to separate during meiosis I or when sister chromatids fail to separate during meiosis II. During gametogenesis, the consequence of nondisjunction during either meiosis I or II is that gametes formed have either an extra chromosome (n+1) or one less chromosome (n-1). Subsequently, fertilization of such gametes by normal gametes yields a trisomic zygote (2n+1) or a monosomic zygote (2n-1) respectively. In anaphase lag, one homologous chromosome in meiosis or one chromatid in mitosis lags behind, is left out of the cell nucleus and eventually undergoes degeneration. Anaphase lag is similar to nondisjunction except that the chromosome or chromatid gets lost, so that one daughter cell has the right number of chromosomes and one daughter cell has one less than normal. This can occur in either of the gametes before fertilization or in the zygote. In the former case, fertilization with a normal gamete will form a zygote with one less chromosome yielding a true monosomic zygote. In the latter case, if anaphase lag occurs after the zygote has already formed, a mosaic, composed of normal cells and monosomic cells, is produced.

Monosomy or trisomy involving sex chromosomes (XXY syndrome, Turner syndrome, Klinefelter syndrome, Multi-X females) are compatible with life and are usually associated with a range of severity of phenotypic abnormalities. Autosomal monosomy generally involves the loss of too much genetic information to permit live birth or even embryogenesis. Conversely, a number of autosomal trisomies do permit survival such as Down syndrome (trisomy 21). With the exception of trisomy 21, all other trisomies yield severely handicapped infants that usually die at an early age.

Mosaicism is a condition characterized by the formation of aneuploid cells that arises when mitotic errors in early development give rise to two or more distinct populations of cells in the same individual. These errors usually occur during the cleavage of the fertilized ovum or in somatic cells. Mosaicism affecting the sex chromosomes is relatively common. For example, in a dividing fertilized ovum, a mitotic error may lead to one of the daughter cells receiving three sex chromosome while another receives only one and can be represented as a 45,X/47,XXX mosaic. All descendent cells from these two precursor cells will accordingly have either a 47,XXX or a 45,X makeup. Depending on the percentage of 45,X cells, this person can potentially further develop to become a mosaic variant of Turner syndrome. Autosomal mosaicism, on the other hand, appears much less commonly than sex chromosome mosaicism. An error during early mitosis that affects the autosomes usually forms a nonviable mosaic with autosomal monosomy. Trisomy 21 is an exception to this rule. Approximately 1% of Down syndrome patients are mosaics, usually having a mixture of cells with 46 and 47 chromosomes. This mosaicism results from mitotic nondisjunction of chromosome 21 during early embryogenesis. Symptoms in such cases are usually milder, depending on the proportion of abnormal trisomic cells.

A separate category of chromosomal aberrations is associated with changes in the structure of chromosomes. Such alterations occur spontaneously at a low rate that is increased by exposure to environmental mutagens. In addition, several rare autosomal recessive genetic

disorders (Fanconi anemia, Bloom syndrome, ataxia-telangiectasia) are highly associated with chromosomal instability and are therefore known collectively as chromosome-breakage syndromes. Also, there is a significantly increased risk of cancers in all these conditions.

Common forms of alterations in chromosome structure include deletions, ring chromosomes, inversions, isochromosomes, and translocations. Deletions refer to loss of a portion of chromosome that may involve either the terminal or interstitial regions. A ring chromosome is produced when a deletion occurs at both ends of a chromosome with fusion of the damaged ends. This might be expressed as 46,XY,r(14). Inversion is a rearrangement that involves two breaks within a single chromosome with inverted reincorporation of the segment. An inversion of only one arm is known as pericentric while breaks on opposite side of the centromere are known a paracentric. Isochromosome formation results when one arm of a chromosome is lost and the remaining arm is duplicated, resulting in a chromosome consisting of only two short arms or of two long arms. In translocations, a segment of one chromosome is transferred to another. In one form, called balanced reciprocal translocation, there are single breaks in each of the two chromosomes, with exchange of material. For example, a balance reciprocal translocation between the long arm of chromosome 2 and the short arm of chromosome 5 would be written 46,XX,t(2;5)(q31;p14). Because there is no loss of genetic material, the individual is phenotypically normal. However, a balance translocation carrier is at increased risk for producing abnormal gametes. Subsequently, fertilization between a carrier and a normal person could lead to the formation of an unbalanced zygote, resulting in spontaneous abortion or birth of a malformed child.

Robertsonian translocations result when the two long arms of acrocentric chromosomes (those with the centromere very near to one end) fuse at the centromere, losing the two short arms, forming a single chromosome (with twice the genetic material), thus having a karyotype with only 45 chromosomes. Common Robertsonian translocations are confined to the acrocentric chromosomes 13, 14, 15, 21, and 22, because the short arms of these chromosomes contain no essential genetic material. Individuals with these translocations are phenotypically normal and carry 45 chromosomes in each of their cells. Their offspring, however, may either be normal and carry the fusion chromosome or they may inherit a missing or extra long arm of an acrocentric chromosome. About 4% of Down syndrome patients have 46 chromosomes, one of which is a Robertsonian translocation between 21q and the long arm of an acrocentric chromosome (usually chromosomes 14 or 22). The translocation chromosome replaces one of the normal acrocentrics but gains an additional chromosome 21 which yields a total of 46 chromosomes with trisomy 21. The karyotype of a Down syndrome patient with a Robertsonian translocation between chromosomes 14 and 21 is 46,XX or XY,rob(14,21),+21. Unlike trisomy 21 caused by nondisjunction, there is no relation between maternal age and the incidence of rob(14,21). However, there is a relatively high recurrence risk in families when the parent, especially the mother is a carrier of the translocation.

Lyonization (X chromosome inactivation): Females have two X chromosomes while males have only one. Thus, one might expect that females should have twice the level of X chromosome proteins and enzymes than males. Empirically, however, this does not happen. The levels are equal in men and women. The reason for this is that in the cells of a human female, one and only one X chromosome is active. The other X coils and condenses into a small ellipsoid structure that is called a Barr body and is functionally deactivated and the genes on that chromosome are not transcribed. The geneticist Mary Lyon hypothesized this almost 40 years ago, so the phenomenon is often called Lyonization. During the very early embryonic development of a female, both her maternal and paternal X chromosomes are active. After 12 days of development, when the embryo has about 5,000 cells, one of these chromosomes is randomly deactivated in all the cells. Once a chromosome is inactive in a given cell, all its daughter cells will have the same chromosome deactivated. That is, if "cell number 23" has the paternal X deactivated, then all descendants of cell 23 will also have the paternal X deactivated. The particular X chromosome deactivated in the original cell is random. Consequently, half of a female's cells will express her paternal X chromosome while the other half will express her maternal X. Thus, females are genetic mosaics.

The gene responsible for X chromosome inactivation, the XIST locus, has recently been localized to the long arm of the X, but the precise mechanism for achieving inactivation is not totally understood. Certain data suggest that the major reason for Lyonization is "dosage compensation"-making certain that the same levels of proteins and enzymes are expressed in males and females. Females with Turner syndrome (only one X chromosome) do not have Barr bodies, females with three X chromosomes have two Barr bodies in each cell, and males with Klinefelter syndrome (two X chromosomes and one Y chromosome) have one Barr body. It appears that the process evolved to guarantee that one and only one X chromosome is active in any given cell. However, inactivation is not totally complete. A few loci of the chromosome comprising a Barr body remain active, most notably those loci homologous to the pseudoautosomal region of the Y chromosome. The fact that inactivation is incomplete is used to explain the phenotypic irregularities for Turner, XXX, and Klinefelter syndrome.

In summary, understanding some common genetic principles permits a better understanding of most genetic disorders. To summarize the case that was initially described, osteogenesis imperfecta (see chapter on connective tissue disorders) is the name given to a group of several different disorders. The severe infantile type is autosomal recessive (an enzyme deficiency) and incompatible with life. The milder adult type is autosomal dominant (a heterozygous structural protein mutation) and compatible with life beyond reproductive age. The autosomal dominant form will probably have a positive family history in one of the parents, and aunts/uncles on the affected parent's side of the family, while the autosomal recessive form will only have a positive family history in siblings. Similarly, Duchenne muscular dystrophy, which is severe, has an early onset, and is often incompatible with reaching reproductive age, is X-linked recessive due to deficiency of the dystrophin protein. Fascioscapulohumeral dystrophy, which is milder, has a later onset, and is compatible with life beyond reproductive age, is autosomal dominant. A positive family history in a parent, aunts, and uncles is likely to be present.

Questions

1. A genetic condition which is lethal in infancy is most likely to be:
    a. An X-linked structural protein.
    b. An autosomal recessive enzyme deficiency.
    c. An autosomal dominant enzyme deficiency.
    d. An autosomal dominant structural protein abnormality.

2. An enzyme deficiency condition can only be inherited in one of two ways:
    a. Autosomal dominant.
    b. Autosomal recessive.
    c. X-linked dominant.
    d. X-linked recessive.
    e. Spontaneous new mutation.

3. The cytologic mechanism(s) by which trisomy 21 (Down Syndrome) can occur include:
    a. Nondisjunction
    b. Robertsonian translocation
    c. Mosaicism
    d. Two of the above
    e. All of the above

4. If there is a family history of genetic disorders, knowing the gender of an unborn child can be important because:
    a. Male children are more likely to have autosomal defects show up in their phenotypes.
    b. Female children are more likely to have autosomal defects show up in their phenotypes
    c. Male children are more likely to have X-linked traits show up in their phenotype
    d. a and c

5. An exchange of fragments of chromatids between non-homologous chromosomes may occur during the first meiotic division. This chromosomal structural abnormality is called:
    a. Deletion
    b. Inversion
    c. Nondisjunction
    d. Segregation
    e. Translocation

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Answers to questions

1. b. An autosomal dominant condition which is lethal in infancy is not going to survive in the gene pool. Such conditions must be autosomal recessive to survive in the gene pool. Most autosomal recessive conditions are enzyme deficiencies. An X-linked enzyme deficiency is also a possible answer, but this is less likely and it is not one of the choices given.

2. b,d. Enzyme deficiencies must be homozygous for the condition to manifest, because a 50% reduction of the enzyme level is generally sufficient to carry out the biochemical reaction involved, such that no clinical disease results. The observed inheritance pattern is autosomal recessive. Enzymes on the X-chromosome such a RBC G6PD are not present on the Y-chromosome, so enzymes can also be inherited in an X-linked recessive fashion. An enzyme deficiency is not likely to manifest from a spontaneous new mutation, because it would have to coincidentally occur in both alleles for this to occur.

3. e. Trisomy 21 results from meiotic nondisjunction in about 95% of patients. About 4% have a Robertsonian translocation. A small percentage of patients are mosaic. An even rarer cause of trisomy 21 is the 21q21q translocation, a chromosome comprised of two chromosome 21 long arms. It is thought to originate as an isochromosome.

4. c. There is a far greater probability of males expressing recessive alleles in their phenotypes if they are carried on X chromosomes. For females to have such traits, they would have to inherit the recessive allele for them on both of their X chromosomes.

5. e. An exchange of fragments of chromatids between non-homologous chromosomes during the first meiotic division is termed a translocation.

Chapter V.1. Common Allergies and Management
Akaluck Thatayatikom, MD

A 12 year old girl presents with a chief complaint of year-round nasal stuffiness and itching eyes for the last 2 years. Her complaints include eyes which are red, watery and itchy; nasal drip (runny nose), congestion, itching, and a poor sense of smell; and sneezing. Her nasal stuffiness bothers her most. Her symptoms disrupt her daily activities and her sleep. Most of these symptoms improve slightly when she takes diphenhydramine and when she is away from home. However, her nasal stuffiness does not change with taking the medication. She has a cat which sleeps in her bed room.

Past history: As an infant she developed egg allergy and an eczematous rash on her face, trunk and extremities. She has no history of asthma. Family history: Both her mother and brother have asthma and hay fever.

Exam: VS are normal. Her height and weight are at the 50th percentile. She has bilateral conjunctival inflammation (redness) with mild chemosis (edema), dusky discoloration of the skin under the eyelids, marked pale swelling of the nasal mucosa which almost completely occludes the nasal airways without evidence of nasal polyps or masses. Both eyes and her nose have whitish clear exudates. Otoscopic examination shows fluid behind both tympanic membranes. She has generalized dry skin with a scatter of hyperkeratotic plaque on both extremities and pityriasis alba of her face.

She is diagnosed with severe persistent allergic rhinoconjunctivitis and otitis media with effusion (OME) with a history of atopic dermatitis and egg allergy. She is treated with a non-sedating antihistamine without significant improvement. Intranasal corticosteroids are added next with minimal improvement. She is then referred to an allergist for evaluation and further treatment. Her skin allergy test is positive to dust mite and cat dander. Her family follows the allergist's recommendations which include: encasing the mattress and pillows in a plastic bag wrap, removing the cat from the house, using an antihistamine with mast cell stabilizing activity (olopatadine) eye drops and allergen immunotherapy. All of her symptoms have gradually decreased with these recommendations. She has currently discontinued all of her medications; except when she exposes herself to cats or house dust (she may require antihistamines as needed).

Symptoms due to allergy commonly occur in children. Atopy refers to a tendency of exaggerated IgE antibody production and is defined by the presence of specific IgE in vivo (skin prick test) or in vitro (RAST test). Atopy represents a predisposition to atopic or allergic diseases including allergic rhinitis, asthma, eczema and food allergy. Scientific evidence of the systemic link between all of the atopic diseases has been increasing recently.

The atopy march starts early in life and most believe that the fetal environment may already be important for both the development of subsequent sensitization and disease manifestation. Early events under the influence of a variety of environmental factors, such as exposure to environmental endotoxin, allergens, infections, and variations in nutrient intake, affect the expression of the atopy genotype. Age of onset of each atopic disease is unique and may be influenced by the mentioned factors. Typically, both atopic dermatitis and food allergy are commonly seen in young infants; while asthma usually starts after 3 years of age, and allergic rhinitis develops in later childhood.

Allergic Rhinoconjunctivitis

By definition allergic rhinoconjunctivitis is a symptomatic disorder of the nose (allergic rhinitis) and eyes (allergic conjunctivitis) resulting from an IgE-mediated immunological reaction following exposure to allergens. Rhinoconjunctivitis is a combined term of rhinitis and conjunctivitis because conjunctivitis is usually accompanied with rhinitis in allergic conditions.

Allergic rhinitis (AR) is extremely common in the general population. The prevalence of AR in the US is about 10-20%. An international study shows that the prevalence of allergic rhinitis varies in different parts of the world from 1%-15% in the 6-7 year-olds and 1%-40% in the 13-14 year-olds. Allergic conjunctivitis (AC), the most common form of ocular allergies, is a self-limited, bilateral inflammation of the eyes.

The nose is a specialized structure with 5 important functions: smelling, resonating for phonation, filtration, heating, and humidification of inhaled air. As a filter for inhaled particles, the nose receives an allergen burden, which per square centimeter is considerably higher than in the lower airways. Its function seems to be the price to be paid for the higher prevalence of AR than other atopic diseases. When airborne allergens come in contact with surface fluid on the nasal mucosa, allergenic molecules are removed within seconds by mucociliary transport and only a small fraction of the allergen molecules will penetrate the epithelial lining since proteins of this size are not easily absorbed from the nasal mucosa. The allergens initiate an allergic reaction when they bind with cell-attached IgE molecules. Mast cells, basophils and Langerhans cells are responsible for the interaction and releasing inflammatory mediators.

Human conjunctiva consist of a nonkeratinized, stratified squamous cell epithelium. The conjunctiva includes goblet cells within the epithelium and overlies the substantia propria, which is composed of connective tissue with cellular elements including mast cells, lymphocytes, macrophages and fibroblasts. One of the highest concentrations of mast cells is at the limbus (the junction of the conjunctiva/sclera and the cornea). The mast cells in the human conjunctiva tend to be centered just beneath the basal epithelial cell layer and around blood vessels. AC is caused by direct exposure of the ocular mucosal surfaces to environmental allergens. The allergic inflammation starts the same as in the nose when allergens bind to the cell-attached IgE molecules and then mediators are released from the cells. Histamine is the principal mediator involved in ocular allergy and inflammation. Most of the allergic reactions are mediated through the effects of histamine on H1 receptors which are found the conjunctiva, cornea, and ophthalmic arteries.

There are two phases of the allergic response in allergic rhinoconjunctivitis: the early phase (minutes to hours) and late phase (6 hours to days). The early phase is induced by mediators such as histamine, prostaglandin, neuropeptides and leukotrienes released by the mast cells. Histamine directly stimulates sensory neurons, inducing pruritus and sneezing, and in concert with the leukotrienes, stimulates the vascular endothelium, inducing vasodilation and increased vascular permeability. Histamine also induces cholinergically mediated reflex glandular secretions, which can be inhibited by atropine or ipratropium. The early phase results in itchy eyes and nose, sneezing, watery eyes, rhinorrhea, edematous conjunctiva and nasal mucosa. After several hours of allergen exposure, other inflammatory cells including eosinophils, neutrophils and activated lymphocytes are demonstrable in the last phase response. The late phase or cellular phase leads to a recrudescence of nasal or eye symptoms associated with a second rise in histamine occurring in some affected persons. Basophils are felt to be responsible for the late-phase histamine peak. Eosinophil activation and accumulation with the release of eosinophilic proteins and mediators are the cause of increasing nasal blockage and hypersensitivity. It results in increasing sensitivity when repeatedly exposed to the same allergens (called the priming phenomenon).

The major symptoms of AR are sneezing, rhinorrhea, nasal pruritus and nasal congestion. There are two common presentations, seasonal and perennial allergic rhinitis. Seasonal allergic rhinitis is characterized mainly by periodic symptoms of the nose, ears, and throat with watery rhinorrhea, nasal congestion, sneezing, and pruritus occurring during the pollination season of the plants (typically, trees in spring, grass in summer and weeds in fall) to which the patient is sensitive. The sneezing, pruritus and rhinorrhea are a main complaint in the seasonal type. Perennial allergic rhinitis is characterized by intermittent or continuous nasal symptoms resulting from indoor allergen exposure (house dust mites, animal fur) without seasonal variation. Nasal obstruction may be the major or sole complaint of the perennial type, particularly in children, in whom the nasal passage is relatively small. Lacrimation, sneezing, clear rhinorrhea and itching of the nose, ears and throat may also occur. The symptoms are less severe than seasonal allergic rhinitis. The decreased severity of the symptoms seen in these patients may lead them to interpret their symptoms as resulting form "sinus trouble" or "frequent colds". In reality, the differentiation of seasonal and perennial types may not be clearly defined. Physical findings of AR often reveal changes in the eyes, nose, ears and throat. A horizontal nasal crease, caused by upward rubbing of the nose due to itching (allergic salute), is usually seen in children. The pale or bluish nasal mucosa with variable degrees of swelling and nasal blockage, and clear watery or yellow nasal secretions may be seen. The appearance of dark circles under the eyes (allergic shiners) is due to venous engorgement secondary to nasal congestion. Periorbital eczema, erythematous conjunctiva with papillary hypertrophy, and gelatinous secretions may appear. Posterior pharyngeal lymphoid hyperplasia secondary to postnasal drip is also noted. Middle ear fluid (otitis media with effusion or serous otitis media) is commonly noted. In some patients, however, the above findings are absent. All of the symptoms may be associated with recurrent sinusitis, asthma or eczema.

The symptoms of AC are watery, itchy, red, sore, swollen, stinging and burning eyes. Corneal symptoms, including photophobia and blurring of vision, are reported in rare cases. The ocular symptoms are frequently associated with nasal and/or pharyngeal symptoms. AC is seldom followed by permanent visual impairment. The presentation can be varied from mild to very severe and can be categorized into seasonal and perennial type. Seasonal allergic conjunctivitis (SAC) is more common and more severe. The onset of symptoms is seasonally related to specific circulating aeroallergens. Grass pollens are more commonly thought to be associated with more ocular symptoms than other aeroallergens. Ragweed is the most common cause of AC accompanying AR. Perennial allergic conjunctivitis (PAC) has symptoms throughout the year. PAC patients may have seasonal exacerbations. Dust mites, animal dander, and feathers are the most common airborne allergens implicated in PAC, which is more likely than SAC to be associated with perennial rhinitis. Both PAC and SAC patients are similar in distribution of age, sex, and associated symptoms of AR, asthma or eczema. Clinical findings of AC include: milky or pale pink conjunctiva with vascular congestion that may progress to conjunctiva swelling (chemosis), a white exudate during the acute state that becomes stringy in the chronic form. The conjunctiva surfaces are mildly injected with various degrees of chemosis. Lid edema sometimes occurs, as well as papillary hypertrophy along the tarsal conjunctival surface (the palpebral surface may appear bumpy). The clinical signs and symptoms are usually bilateral, although the degree of involvement may not be symmetrical.

The diagnosis of allergic rhinoconjunctivitis is based on a detailed history and physical findings as mentioned. Many allergic patients do not report the ocular or nasal symptoms unless they are asked directly about them during a medical examination. When evaluating patients who present with significant nasal symptoms, the following questions should be asked:

1. Is the nasal congestion or sneezing/itching/runny nose a main concern? Are there eye symptoms?
2. Does an activity or allergen exposure or a specific environment contribute to the symptoms? Seasonal or year-round symptoms? What are the clinically relevant allergens?
3. Are there other atopic diseases in the patient or the family?
4. Were any medications including topical OTC preparations (nasal and eye drops) used in the past?
5. Do the symptoms cause a major impact on lifestyle such as school activity or sleeping?

Typically, patients with classic symptoms do not require any tests. Slightly elevated serum IgE, mild peripheral blood eosinophils and eosinophilia of the nasal secretions are common findings; but these results are not diagnostic. Allergy testing including skin testing or radioallergosorbent test (RAST) may be required for the diagnosis and guidance of environmental avoidance in some patients with uncontrollable disease or atypical presentations. The allergy tests in young children are limited because positive specific IgE or skin prick tests to inhaled allergens usually develop after the second year of life.

Skin testing is the most common test for the diagnosis of allergy because of its simplicity, high sensitivity, low cost and rapidity of the result. Prick testing is widely used by allergists since the test is quick, not painful, inexpensive, highly specific with a low risk of systemic reaction. Prick testing requires: 1) devices such as metal needles or lancets or commercial test devices, 2) allergen extracts, 3) positive controls (histamine) and negative controls (glycerin or saline). A physician and equipment for treating anaphylaxis reaction should be readily available while performing the test. Patients should be instructed to discontinue some medications inhibiting skin response for a period of time including tricyclic antidepressants (5 days), hydroxyzine (3 days), astemizole (60 days), and other antihistamines (3 days). Contraindications for skin tests are generalized skin disease, inability to discontinue antihistamines, history of severe reactions or anaphylaxis to previous skin testing, pregnancy, dermatographism, unstable angina and beta-adrenergic receptor agent therapy (beta blockers, beta agonists or both). A response to an allergen with a wheal size greater than 3 mm in diameter indicates a positive result and having a specific IgE to the allergen. If the skin prick result is negative, an intradermal skin test may be considered in a highly suspected patient since the intradermal skin test is more sensitive.

RAST is an in vitro test for specific IgE antibodies based on the principle of immunoabsorption . This in vitro test for allergy is a convenient allergy test for non-allergist physicians or for patients who have contraindications for skin testing. RAST is not as sensitive as the skin test in most instances. Appropriate in vitro tests correlate up to 70-80% of the time with prick skin tests. CAP-RAST testing (a type of RAST test) is preferred over other RAST tests because of better standardization.

The differential diagnosis of allergic rhinoconjunctivitis includes infectious rhinoconjunctivitis, which includes the common cold, usually caused by rhinovirus, RSV, parainfluenza virus, influenza virus and adenovirus. Fever, sore throat, thick purulent rhinorrhea or eye discharge, erythematous nasal mucosa, and the presence of cervical lymphadenopathy are helpful differential findings in infectious rhinitis. Common diseases that may be confused with perennial allergic rhinitis are recurrent infectious rhinitis, chronic sinusitis, and vasomotor rhinitis. Structural and mechanical conditions that may mimic perennial allergic rhinitis include a deviated nasal septum, hypertrophic turbinates, adenoid hypertrophy, foreign bodies and tumors. Inflammatory and immunologic diseases such as Wegener's granulomatosis and sarcoidosis may present with rhinitis symptoms. Nasal polyposis, an uncommon condition causing nasal congestion in children, is usually associated with cystic fibrosis, asthma and aspirin intolerance and predisposes to sinusitis.

Nonallergic rhinitis with eosinophilia (NARES) may be misdiagnosed as allergic rhinitis. NARES is not IgE dependent and is not associated with high IgE levels or positive skin tests. Symptoms in NARES are more likely to be induced by exposure to irritants, strong

odors, cold air, and cigarette smoke. Drug-induced rhinitis is associated with use of various oral agents, especially certain classes of antihypertensive beta- blockers, oral contraceptives, chlorpromazine, aspirin and overuse of topical (nasal drops and sprays) sympathomimetics (rhinitis medicamentosa). Other less-common causes of rhinitis include occupational exposure, hormones, food and alcohol.

Several eye diseases need to be differentiated in patients with allergy and ocular symptoms. Irritative and chemical conjunctivitis is commonly confused with AC. The main symptom caused by environmental pollutants and smoke is conjunctival hyperemia. Atopic keratoconjunctivitis typically occurs in patients with atopic dermatitis. It is a bilateral, sight-threatening disease and symptoms are much more severe than SAC and PAC. The symptoms include significant itching, burning and redness, eventual fibrosis, decreased keratinization of conjunctival surfaces, cataract formation and lid malposition. Vernal keratoconjunctivitis is a chronic form of allergic conjunctivitis characterized by large "cobblestone" papillae on the underside of the eyelid. The symptoms are intensely pruritic and sight-threatening. Giant papillary conjunctivitis, a non-allergic condition, may be confused with ocular allergy. Giant papillae on underside of eyelid and non itching are distinguishing symptoms.

The management of allergic rhinoconjunctivitis in children includes allergen avoidance and education, medications and allergen immunotherapy as in adults. Allergen avoidance and environmental control are the main stay of treatment in all age groups.

Allergen avoidance and environmental control:

A wide range of allergens have been associated with allergic rhinoconjunctivitis, of which house dust mites are clearly the most important. The single most effective strategy for reduction of dust mite exposure involves bed-covering systems, which separate the mite allergens from the allergic individual by encasing mattress, pillows and blankets with mite allergen impermeable covers. Other recommendations for dust mite control are: 1) Washing the blankets, bed linen or other washable material such as curtains and toys in hot water over 55 degrees C regularly once a week. 2) Removing children's soft toys or washing/freezing the toys once a week. 3) Removing and replacing carpet in the house with vinyl or polished wooden floor boards. If it is impossible to remove the carpet, the carpet can be completely covered by polyethylene sheeting. 4) Mite control (acaricide) sprays have demonstrated some effects in reducing mite numbers and allergen levels. However, the clinical efficacy demonstrates only reducing symptom scores but not medication use. 5) High efficiency particulate air (HEPA) vacuum cleaners can reduce allergen load but no trial has demonstrated that this will improve symptoms.

Cat and dog fur is one of major allergens implicated in causing the perennial type. The allergens are not the dander itself but are contained in the saliva and in sebaceous secretions, which can flake off in small particles and remain airborne for considerable periods of time. This results in a ubiquitous allergen that can be found in many public places, even in a cat-free or dog-free buildings and schools. It makes avoidance much more difficult. The only effective measure for avoiding the allergens in the home is to remove the pets, carefully vacuum and clean all carpets, mattresses and upholstered furniture. Frequent washing of cats may reduce allergen exposure. However, clinical studies have not shown a clear benefit from this procedure when carried out once a week. A placebo-controlled trial of a HEPA air cleaner in the treatment of cat allergy did not find a significant effect on rhinitis.

Indoor molds can be removed with a bleach solution and can be followed by measures to reduce local moisture or humidity such as using a dehumidifier. Outdoor allergens, such as pollens, grass and fungal spores, are difficult to avoid. Outdoor exercising in the morning for sufferers with pollen allergy is recommended. These sufferers should be reminded to keep their bedroom window closed during the daytime and open windows only at night when the pollen count is low.

Medical treatment for allergic rhinitis:

It should be noted that there are only a few medications that have been tested in children under the age of two years. In young children under the age of four, use of nasal saline drops or spray can simply comfort them and help to clear their nose before eating or sleeping. Several concerns of medical treatment in children have been raised. The most important aspects are the antihistamine side effects on the cognitive functions of pre-school and school children. The use of systemic corticosteroids such as oral or depot-preparations should be deferred due to their systemic adverse effects. Children with allergic rhinitis who are athletes should be advised about the medications used since some of these medications are prohibited by various sports organization. Alpha-adrenergic agonists and systemic decongestants (both often combined with H1-antihistamines) are often prohibited in organized youth sports since they have a central stimulant effect. For intranasal corticosteroid use, a medical certificate documenting medical necessity should be issued. However, the regulations vary between countries, so physicians treating the athletes should be aware of these regulations.

All H1 antihistamines are competitive antagonists of histamine and are rapidly absorbed from the gastrointestinal tract. Antihistamines are most effective for sneezing, pruritus and rhinorrhea. They exert little effect on nasal congestion. Therefore, as a rule, they are more effective in acute, seasonal allergic rhinitis than in the perennial form in which congestion or stuffiness is usually more prominent. The use of H1-antihistamines is important for the treatment of rhinitis in children. The response to different antihistamines may differ from patient to patient, but it has been demonstrated that children not responding to one antihistamine may respond to another.

Antihistamines have been classified into first and second generation families. Some of the commonly used first generation antihistamines are triprolidine, diphenhydramine, chlorpheniramine, azatadine and hydroxyzine. All of them except hydroxyzine are over-the-counter medications (OTC). The first-generation antihistamines cause drowsiness, reducing one's ability to concentrate, blunting cognitive functions to some extent, and have varying anti-muscarinic effects such as dry mouth, constipation, blurring of vision, urinary retention. Their adverse effects limit their utility. Their use should be restricted to two relatively uncommon situations: 1) Children with urticaria or atopic dermatitis whose pruritus is so severe that the sedation produced by an old H1-antagonist, such as diphenhydramine or hydroxyzine, is a benefit rather than a risk. 2) Children with anaphylaxis who require intravenous diphenhydramine as adjunctive treatment to epinephrine and other medications.

Second-generation antihistamines are recommended for seasonal AR. Currently available forms include:

azelastine (Astelin): nasal spray, BID.
cetirizine (Zyrtec): low sedating, PO, once daily.
loratadine (Claritin): non-sedating, PO, once daily.
fexofenadine (Allegra): non-sedating, PO, BID.
desloratadine (Clarinex): non-sedating, once daily.

Only cetirizine and desloratadine are approved by FDA for perennial allergic rhinitis. Loratadine and fexofenadine are less sedating (minimal or no drowsiness). The above oral antihistamines are available as a combination medication with pseudoephedrine (Zyrtec-D,

Claritin-D, Allegra-D) since antihistamines have little effect on congestion. However, the use of an antihistamine with decongestant is limited to children older than 12 years. Desloratadine (Clarinex) is a non-racemic form of loratadine.

Intranasal corticosteroids ("steroids" for short) have proved to be the most effective class of drugs in reducing the symptoms of allergic rhinitis. This clinical response reflects the broad anti-inflammatory activity and multiple pharmacologic actions of corticosteroids. They have demonstrated specific effects on decreasing the activity of inflammatory cells such as mast cells, basophils, eosinophils, Langerhans' cells and decreasing the levels of chemical mediators including histamine, Th2 cytokines, chemokine and adhesion molecules. A single dose of intranasal steroid administration blocks the late-phase response; whereas repeated dosing blocks both early and late response, as well as the priming phenomenon. Intranasal steroids reduce the specific IgE production in seasonal allergic rhinitis and decrease nasal hyperresponsiveness or the priming phenomenon.

Intranasal steroids have been considered as second line agents after antihistamines by many physicians; however, first-line use of intranasal steroids is becoming increasingly common, especially for patients with moderate to severe symptoms. Intranasal steroids are more efficacious in chronic symptom relief than oral antihistamines, decongestants and cromolyn except for eye symptoms. Regular use of intranasal steroids is more effective than intermittent p.r.n. use, but p.r.n. use does have some efficacy in many patients. Although no well controlled study of a combination use of steroids and other medications is published, in clinical practice, intranasal steroids can be used in combination with other therapies to achieve optimal improvement in overall symptoms.

Several intranasal steroids are available including beclomethasone (Beconase, Vancenase), flunisolide (Nasarel), triamcinolone (Nasacort), budesonide (Rhinocort), fluticasone (Flonase) and mometasone (Nasonex). After using the recommended dosage for 2 weeks, the patient should be reevaluated, and the dosage can be adjusted based on the clinical response. The goal of therapy should be to use the lowest dosage that provides effective relief of symptoms. With proper use of intranasal steroids, 60-90% of patients may have nearly complete relief of rhinitis symptoms.

The most frequently observed adverse effect with intranasal steroids is local irritation. Approximately 10% of patients have some form of nasal irritation, nasal burning or sneezing after administration. Bloody nasal discharge occurs in approximately 2% and a few cases of septal perforation were reported due to improper techniques of administration. Long-term use of intranasal steroids does not appear to cause a significant risk of adverse morphologic effects on the nasal mucosa. Systemic side effects of intranasal steroid are rare, such as growth suppression due to low systemic absorption. Generally, the systemic absorption can occur through direct intranasal absorption or through gastrointestinal absorption of the swallowed fraction of the administered dose. It is likely that approximately 80% of the administered intranasal dose is swallowed resulting in systemic absorption. Mild growth suppression may result from chronic use of beclomethasone since it is metabolized to another active steroid compound.

Cromolyn sodium (Nasalcrom) has been one of the common drugs used for AR in children. It inhibits mast cell mediator release, and may inhibit C-type sensory nerve fiber transmission which modulates vascular and glandular responses. The drug is effective only when applied topically to the mucosal surface of the allergic end organ. It cannot be used orally for allergic disease. Cromolyn has been shown in numerous studies to be effective for both types of AR. It has a greater benefit in seasonal type symptoms and in highly allergic persons.

The major advantage of cromolyn is its safety, since there are no significant side effects of this drug. Its major drawback is the Q.I.D dose. In addition, it must be used on a regular basis to be effective, and ideally should be started before the onset of the symptoms. In patients with the seasonal type, cromolyn is best initiated just before the season starts at a dose of one spray in each nostril four times daily, and is continued throughout the season. In patients with perennial type, it can be started at any time, but it may take a few to several days to be effective. The recommended dose is one to two sprays in each nostril four times daily. After a patient's symptoms have stabilized, the dose may be decreased to three times daily, with increases to four times daily if symptoms worsen. Patients who are allergic to known triggers, such as animals, can use two sprays of cromolyn in each nostril 30 minutes before allergen exposure to prevent an allergic reaction.

Montelukast (Singulair), a leukotriene receptor antagonist given orally, has a new indication to be used for seasonal allergic rhinitis. Its efficacy might be equal to oral antihistamines (more data are needed), but it is less effective than intranasal corticosteroids and more expensive than both.

Nasal ipratropium (Atrovent), a topical anticholinergic nasal spray, is useful in patients with both allergic and non allergic rhinitis who experience rhinorrhea from various other triggers (e.g., cold air, eating spicy foods, and other irritants), by controlling rhinorrhea induced by nonspecific activation of cholinergic receptors. Its effectiveness is limited in patients with moderate to severe allergic rhinitis because ipratropium has little effect on other symptoms, such as sneezing, pruritus, or congestion. It is commonly used as an adjunct therapy if the rhinorrhea symptoms still persist with the antihistamine or intranasal steroid treatment. It is recommended for use in children older than 6 years. Common adverse effects are drying of the nasal mucosa and mild epistaxis.

Adrenergic nasal decongestants are available in both topical forms (e.g., oxymetazoline, phenylephrine and propylhexedrine) and oral forms (e.g., pseudoephedrine, phenylpropanolamine). The decongestants increase nasal patency by inducing vasoconstriction and reducing tissue swelling and obstruction. Although the decongestants have been used in children for years, there are very few studies in these young patients. The decongestants can be useful initially, often coupled with an antihistamine to control active allergic rhinitis symptoms. Once control is achieved, further symptoms usually can be prevented by the judicious use of antihistamines alone or with a nasal corticosteroid.

Decongestants should be deferred in small children and in patients who currently take MAO inhibitors. The side effects of oral decongestants are nervousness, dizziness, tachycardia, shakiness, urinary retention, insomnia. Its long-term round-the-clock use may increase the risk for hypertension. There is an association of hemorrhagic stoke and phenylpropanolamine (PPA) use in adults. Therefore, PPA was removed from the market by the FDA in November 2000. The major concern of nasal decongestants is the prolonged use which may induce rhinitis medicamentosa (especially with topical decongestants), which is rebound mucosal swelling from withdrawal of the medication. This discomfort may prompt the patient to use the medication frequently to avoid a sense of smothering. Ultimately, this cycle can induce serious irreversible mucosal damage. Therefore, topical preparations should be used for not more than 3 to 5 consecutive days to prevent rhinitis medicamentosa.

A guideline of treatment for allergic rhinitis: Recently, an expert panel in association with the World Health Organization (WHO) has recommended a guideline for the medical treatment of AR based on clinical severity ("mild" or "moderate-severe"). The severity is further subdivided into "intermittent" or "persistent" according to the duration of symptoms. It is necessary to define the severity of the allergic individual, then the choices of medications are based on the severity:

"Mild" means that none of the following items are present: sleep disturbance, impairment of daily activities (leisure and/or sport), impairment of school or work, troublesome symptoms. "Moderate-severe" means that one or more of the above items is present and a disturbance or impairment exists which not found in "mild". "Intermittent" means that the symptoms are present for less than 4 days a

week or for less than 4 weeks. "Persistent" means that the symptoms are present more than 4 days a week or for more than 4 weeks. Treatment recommendations are as follows:

For mild intermittent disease: oral or intranasal H1 antihistamines or intranasal decongestants (for less than 10 days and not to be repeated more than twice a month) or decongestants (not recommended in children less than 12 years old).

For moderate-severe intermittent disease: oral or intranasal H1 antihistamines or oral H1-antithistamines or decongestants or intranasal steroids or cromolyn sodium .

For mild persistent disease: Same medications as for moderate-severe intermittent above. The patient should be reassessed after 2 to 4 weeks. A stepwise approach is advised. If the patient has persistent mild symptoms and is on an H1-antihistamine or cromolyn treatment, changing the medication to an intranasal steroid is suggested. The dosage of intranasal steroids may be reduced by half if the patient responds well to the treatment. In seasonal allergy, a shorter course of treatment is required depending on the pollen season. However, long-term treatment may be needed especially in perennial allergy.

For moderate-severe persistent disease: Intranasal steroids are the first line treatment. The patient should be reassessed after 2 to 4 weeks of the treatment. A stepwise approach is advised. If the patient does not improve, consider other reasons for failure to respond to the treatment including heavy persistent allergen exposure (e.g., cat on the bed), inadequate medication compliance, nasal obstruction preventing drug delivery, other additional nasal pathology such as nasal polyps, sinusitis or nasal septal deviation, and a wrong diagnosis. If the major symptom is blockage, doubling the dose of the intranasal steroid is suggested. Add an H1-antihistamine if the symptoms of sneezing, itching or rhinorrhea still exist. Add ipratropium if rhinorrhea is not improved. If the patient's symptoms are less, a step down approach should be used. However, the treatment should last for at least three months or for the duration of the pollen season. In the step down treatment, a low dose of intranasal steroid may be required as a maintenance treatment to control symptoms. Referral to a specialist may be considered if the treatment is not fully effective, or if the duration of the treatment is over 3 months and the medications are not helpful.

Medical treatment of allergic conjunctivitis:

The primary goal of medical treatment is to alleviate the ocular symptoms and signs which disrupt the patient's quality of life. Initial management with allergen avoidance, cold compresses, and lubrication (artificial tears) should be tried before ocular agents are tried. Cold compresses provide considerable symptomatic relief, especially from ocular pruritus and swelling. In fact, all ocular medications provide additional subjective relief when applied immediately after refrigeration. Tear substitutes consisting of saline solution combined with a wetting and viscosity agent, such as methylcellulose or polyvinyl alcohol, can be applied topically 2 to 4 times a day and as needed. It is a soothing, effective, convenient and inexpensive option which directly removes and dilutes allergens that may come in contact with the conjunctiva.

Oral antihistamines used for the treatment of systemic or nasal allergy can reduce but do not eliminate the eye symptoms. However, treatment with oral antihistamines, especially the first generation, may cause eye dryness which interferes with the ocular defense mechanism and increases the potential for ocular irritation and sensitivity. The use of a "topical" agent on the affected eyes is the easiest and most direct therapeutic method. An important consideration for effective topical treatment is compliance. Treatments causing ocular irritation are likely to diminish compliance and may lead to a chronic duration of the condition, decreased patient satisfaction, and increased ocular sensitivity. Efficacy of these agents varies from patient to patient, and the choice of agent used will depend on the underlying health of the eye and other variables, such as drug cost, contact lens wear, and compliance. Several topical agents are available for the treatment and the prophylaxis of ocular allergies. These include vasoconstrictors, antihistamines, mast cell stabilizers, and anti-inflammatory agents.

OTC topical antihistamines are widely used in combination with topical vasoconstrictors. The combination is more effective than either agent alone or a systemic antihistamine. Adverse effects of topical vasoconstrictors include burning and stinging on instillation, mydriasis, rebound hyperemia or conjunctivitis medicamentosa with chronic use and drug interaction with MAO inhibitors. Topical vasoconstrictors are contraindicated in patients with narrow angle glaucoma.

Topical prescription antihistamines, including levocabastine, emedastine and azelastine, are a good option for symptomatic relief of an ocular allergy. Since these agents do not provide mast cell stabilization, they do not prevent or treat a significant cause of the allergy. All of the topical antihistamines require dosing as frequently as every 4-6 hours, except azelastine which requires only BID dosing, which may improve compliance.

Topical mast cell stabilizers include cromolyn, nedocromil, lodoxamide and pemirolast. It should be noted that the medications require several days (3-5 days) to start providing symptomatic relief of ocular allergy. The relief reported within 15 minutes probably represents a "washout" effect immediately after contact with the eyes. Long term use of these agents is necessary since they are preventive only. These agents require Q.I.D. administration with the exception of nedocromil which is B.I.D.

Topical dual action antihistamine and mast cell stabilizers include ketotifen and olopatadine. Therefore, they have rapid onset and prolonged duration of action. Both of them are approved for twice a day dosing for treating AC in children 3 years and older. Topical ketorolac (a nonsteroidal anti-inflammatory agent) is approved for use in children 12 years and older with acute SAC. It inhibits allergen induced prostaglandin production which diminishes the ocular itching and conjunctival hyperemia. Local administration of topical corticosteroids is associated with localized ocular complications such as viral infection, elevated intraocular pressure and cataract formation. Therefore, routine use is not recommended and their use should be under the close supervision of an ophthalmologist.

Allergen immunotherapy (AIT) is a safe and effective treatment for long-term control of allergic rhinoconjunctivitis. AIT is considered when environmental control is limited, when medications are ineffective or not well tolerated, or when the symptoms are a significant trigger for other chronic problems such as asthma or sinusitis. AIT results in successful treatment of AR in 85%-90% of cases. It is also recommended as a treatment for venom or insect hypersensitivity and selected cases of asthmatics. Patients with chronic urticaria, atopic dermatitis, or food allergy do not benefit from AIT. AIT induces immune tolerance to the specific allergens. In many cases, AIT can prevent clinical progression of allergic disease and may minimize the development of sensitization to multiple allergens in patients who are sensitized to a single allergen. The terms, "allergen vaccination" and "allergen immunotherapy", can be used interchangeably.

Prior to considering AIT, the patient must have evidence of specific IgE sensitivity such as a positive skin test or RAST test. Small doses of allergen extracts to which the patient is sensitized, are administered subcutaneously. The injected dose can be gradually increased as in a conventional AIT or rapidly increased as in a rush AIT until the maintenance dose is reached. The goal is to blunt the immune response with an optimal dose.

The efficacy of AIT for common allergens including house dust mite, cat, cockroach, birch, grass, and ragweed pollens have been well-documented. The efficacy of AIT depends on the quality of the allergen extract, the duration, the frequency of administration, the relevant allergens and the allergen doses. The dose of specific protein delivered in an allergen extract is crucial for induction of immune tolerance. If the extract is highly diluted or there are too many allergens which result in reduction of the relevant allergen dose, it will compromise the efficacy. In low doses, AIT is not effective in most patients. Therefore, a high dose of allergen extract per injection must be achieved as a maintenance dose to provide significant clinical benefit.

Allergic rhinoconjunctivitis causes substantial morbidity although the disease is not associated with mortality. Many physicians do not pay attention to the disease because they underestimate the impact of allergic rhinoconjunctivitis on other diseases, quality of life and performance. AR is a common cause of asthma exacerbation or uncontrolled persistent asthma. It is estimated that up to 90% of children with asthma have respiratory allergies, especially to indoor allergens such as house dust mite, Alternaria species, cockroach, or cat. All asthmatics should be evaluated for allergic rhinitis. Untreated or undertreated allergic rhinitis is associated with the development of otitis media with effusion (OME) and sinusitis. The OME may result in hearing impairment, which worsens progressively as the symptoms continue. There is strong evidence that AR and atopic dermatitis are more common in children with OME compared with normal subjects. Therefore, children with OME should be assessed for allergic rhinoconjunctivitis and children with allergic rhinoconjunctivitis should be assessed for OME. Adverse effects of allergic rhinoconjunctivitis in children are school absences, poor performance, poor concentration, headaches, malaise, and lethargy as a consequence of sleep disturbance and therefore reduced ability to learn. Furthermore, many of the antihistamines employed have some sedating effects, thereby aggravating the problem.

Although genetic factors contribute to the risk of allergic disease development, it is likely that environmental factors are partially responsible for the increase in the prevalence of atopic diseases. Therefore, changing the surrounding environment or other factors may decrease or prevent the atopic diseases. The following measures are recommended:

1. Raising children in a smoke-free environment, starting in utero.
2. Breast feeding for 4-6 months, delaying the introduction of solid food until 6 months of age, and withholding highly allergenic foods such as egg and peanut for 2 to 3 years, especially in a highly allergic family.
3. Reducing exposure to environmental allergens, especially in patients who have already developed respiratory allergies.

A hygiene hypothesis is supported by some studies. This hypothesis implies that overcrowding and unhygienic contacts early in life may protect from atopic diseases. The changes of human microbial flora, declining exposure to food-borne and orofecal infections, to helminths and to environmental sources of endotoxin are putative contributors to the rise of allergy cases among populations living with a western lifestyle. Lifestyle or clinical recommendations based on this hygiene hypothesis still remain to be proven.

Questions

1. The most prevalent of allergic disease in school-age children is:
    a. Atopic dermatitis
    b. Food allergy
    c. Asthma
    d. Allergic rhinitis
    e. Drug allergy

2. A 15 year-old has had persistent year-round nasal itching and stuffiness. What is the most likely allergen responsible for the symptoms?
    a. Dust mite
    b. Weed
    c. Tree
    d. Grass
    e. Mold

3. Which one is the most effective method for controlling dust mite exposure?
    a. Encasing mattresses, pillows and blankets
    b. Spraying an acaricide agent in the house
    c. Using HEPA air filter and vacuum
    d. Removing furniture and carpet in the house
    e. Washing washable materials in hot water

4. The most effective measure for allergen avoidance in furred animal allergy is:
    a. Washing the animal twice a week.
    b. Using HEPA air filter and vacuum in the house.
    c. Limit areas of the animal in the house.
    d. Removing furniture and carpet in the house.
    e. Removing the animal from the house.

5. Which one is the appropriate medical treatment of an 8 year old girl who develops nasal allergy in spring season?
    a. Diphenhydramine
    b. Cetirizine
    c. Fexofenadine with pseudoephedrine
    d. Nasal decongestant spray
    e. Beclomethasone nasal spray

6. The most effective and appropriate for a child with chronic allergic rhinitis and nasal stuffiness is:
    a. Intranasal antihistamine
    b. Intranasal corticosteroid
    c. Intranasal decongestant
    d. Oral antihistamine
    e. Oral antihistamine and decongestant

7. Which one is the most common adverse effect of intranasal steroids?
    a. Nasal irritation
    b. Septal perforation
    c. Nasal bleeding
    d. Short stature
    e. Adrenal suppression

8. Which one of the diseases benefits from allergen immunotherapy?
    a. Food allergy
    b. Atopic dermatitis
    c. Allergic rhinoconjunctivitis
    d. Latex allergy
    e. Chronic urticaria

9. Which one of the following eye drops has both antihistamine and mast cell stabilizer properties?
    a. Naphazoline
    b. Levocabastine
    c. Cromolyn
    d. Olopatadine
    e. Rimexolone

10. A mother of children with multiple allergic diseases asks you for allergy prevention advice for her next child. What would you recommend?
    a. Smoking free environment
    b. Breast feeding at least 4 months
    c. Diet control during pregnancy
    d. Using HEPA air filter and vacuum
    e. Both a and b

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Answer to questions

1.d, 2.a, 3.a, 4.e, 5.b, 6.b, 7.a, 8.c, 9.d, 10.e

Chapter V.2. Anaphylaxis and Other Acute Allergic Reactions
Todd T. Kuwaye, MD, MS

A 12-year-old boy is brought to the emergency department after being stung by a bee. He had been well until he was stung on his right forearm, while playing in the yard. He initially complained of localized pain and swelling. Fifteen minutes later, he began to complain of shortness of breath. His parents observed him to be wheezing. He also said that he felt very weak and dizzy. His parents brought him immediately to the local emergency department.

Exam: VS T 37.1, P 120, R 39, BP 69/45. He is in mild respiratory distress. He is drowsy and pale, but awakens when you talk to him. He has generalized urticaria. He has no conjunctival edema. His lips and tongue are not swollen. His voice sounds normal. Heart tachycardic without murmurs. His lung examination shows mild wheezing and fair aeration with minimal retractions. His abdomen is soft and non-tender. His face is moderately pale. The bee sting site on his right forearm is unremarkable with no foreign body seen.

He appears to in early anaphylactic shock and he is immediately given subcutaneous epinephrine and an albuterol updraft with improvement of his symptoms. An IV is started, but since his condition is improving, he is not given IV epinephrine. He is given diphenhydramine IV, cimetidine IV, methylprednisolone IV, and an IV fluid bolus of normal saline. His urticaria resolves, his blood pressure normalizes and his lungs sound clear. After being observed in the ER for three hours, he feels as if he is back to normal. He is discharged from the ER on oral diphenhydramine and prednisone.

Anaphylaxis is a clinical syndrome involving the circulatory and respiratory systems. There are no specific criteria for anaphylaxis. Anaphylaxis is a word that is poorly defined. According to one dictionary, it means an exaggerated allergic reaction, while others have defined anaphylaxis as being more severe, involving the respiratory and/or cardiovascular systems. Allergists and immunologists define anaphylaxis as an immediate systemic reaction caused by IgE mediated release of potent mediators from tissue mast cells and peripheral blood basophils. This definition, however, does not allow the clinician to differentiate anaphylaxis from other less severe allergic conditions. This definition does differentiate anaphylaxis from anaphylactoid reactions, but to the physician this is arbitrary since both will be managed the same. Most clinicians will agree that anaphylaxis is a severe, potentially life-threatening allergic response to a repeat exposure to an allergen. Symptoms may include swelling, urticaria, angioedema, hypotension, bronchospasm, airway obstruction/edema, shock, loss of consciousness and ultimately death if help is not received.

Due to a lack of specific clinical criteria for anaphylaxis there is no accurate data on its occurrence. In the United States, it is estimated that more than 40 people per year die from insect sting anaphylaxis (1).

Clinical manifestations include rapid onset of symptoms, a feeling of impending doom, weakness, dizziness, confusion, loss of consciousness and seizures. Airway and pulmonary findings include congestion, sneezing, rhinorrhea, swelling of the lips and tongue, stridor, hoarseness, dyspnea and wheezing. Cardiovascular findings include light headedness, syncope, tachycardia, hypotension, pallor, arrhythmia and complete cardiovascular collapse. Cutaneous findings include erythema, flushing, pruritus, angioedema and urticaria. GI findings include: nausea, emesis, abdominal cramping and diarrhea. Patients with anaphylaxis may have any combination of the above.

After the onset of the initial symptoms, symptoms may recur despite initial treatment. This recurrence of symptoms has been called biphasic anaphylaxis. In adults, the rates of biphasic anaphylactic reactions are between 5-20% and in children 6% (2,3). The differential diagnosis for anaphylaxis includes asthmatic attacks, vasovagal reactions, Scombroid fish poisoning (a histamine reaction), hereditary angioedema, systemic mastocytosis, vocal cord dysplasia, shock, metastatic carcinoid, serum sickness, panic attacks as well as the less severe acute allergic reactions.

Etiologies of anaphylaxis include food, insect stings, antibiotics, vaccines, latex and idiopathic causes. Common foods that trigger anaphylaxis include tree nuts, peanuts, shellfish and dairy products. The pathogenesis of anaphylaxis involves prior exposure to an allergen (such as mentioned above). Upon first exposure of the offending allergen, a specific IgE antibody is produced against the allergen. These IgE antibodies attach themselves to the outer surface of mast cells. Upon re-exposure to the offending allergen, the allergen complexes with the IgE antibodies on mast cells. This interaction between the specific IgE antibody and the allergen sets into motion the degranulation of tissue mast cells and blood basophils. The mast cell releases potent inflammatory mediators such as histamine, proteases and chemotactic factors such as tumor necrosis factor. In addition to these primary mediators, there are secondary mediators such as prostaglandins and leukotrienes that are also produced. These potent mediators have the effect of producing the symptoms of anaphylaxis. The main inflammatory mediator is histamine, which causes initial erythema (vasodilatation), edema (vasopermeability) and secondary flare (axon reflex with arteriolar dilation) (4). Anaphylactoid reactions produce a similar inflammatory response, but the primary difference is that the reaction is not IgE mediated. Examples of anaphylactoid reactions are those caused by radiocontrast media, anesthetics, and exercise.

The diagnosis of anaphylaxis is made clinically. Thus, it is important to rule out disorders mentioned in the differential diagnosis. There is some evidence that measuring a serum tryptase within 2 hours of an anaphylactic episode is helpful to diagnose anaphylaxis. However, the test is not available and is limited to research labs. The difference between anaphylaxis and anaphylactoid reaction to the clinician is not important since both are treated the same.

The primary immediate treatment of anaphylaxis is epinephrine. If a patient has a history of a previous severe reaction, then it is recommended that the epinephrine may be given immediately after contact or ingestion, with no waiting periods to see if a severe reaction will occur (5). Pediatric dosage for epinephrine is 0.01mg/kg up to a max dose of 0.5mg per dose or 0.5ml of 1:1000 SQ/IM Q15minutes for two doses and then Q4 hours as needed. The adult dosage is 0.2-0.5ml of a 1:1000 epinephrine solution. IM administration is faster than subcutaneous (SQ) (6). IV epinephrine is given for severe reactions in which patients are in severe shock. When in severe shock, the skin and muscle may not be adequately perfused, so SQ or IM epinephrine will not be absorbed sufficiently in the circulation unless it is given IV. It is usually recommended to prepare a dilute infusion of epinephrine calculated as 0.1 to 1.0 mcg/kg/min. This is cumbersome, time consuming and impractical for the patient who needs IV epinephrine immediately. Another practice is to utilize the 1 mg 1:10,000 epinephrine injector (1 mg diluted in 10cc), and inject this very slowly into the IV line, allowing the clinician to titrate the dose. Epinephrine is a dangerous drug, which will cause severe palpitations and/or dysrhythmias if it is given too fast. You could calculate the SQ/IM dose and administer only this dose IV between 2 to 10 minutes depending on the severity of the patient.

Patients with a previous history of anaphylaxis are usually given epinephrine autoinjectors for home use (e.g., EpiPen 0.3 mg, EpiPen Junior 0.15 mg). All patients receiving epinephrine should immediately go to the emergency department or call 911 (5).

Adjunctive therapy for anaphylaxis includes antihistamines. H1 blockers appear to be effective. Diphenhydramine (H1 blocker) is the most commonly used drug given parenterally. A combination of H1 and H2 blockers (such as diphenhydramine and cimetidine) given

together may have more benefit than a single antihistamine in treating severe allergic reactions (7). However no study has shown the addition of H2 blockers to provide additional benefit in the treatment of anaphylaxis. Corticosteroids are not effective in the treatment of anaphylaxis in the acute period. There is some discussion that it may be effective in the biphasic phase of anaphylaxis. Although corticosteroids are commonly given in anaphylaxis and other severe allergic reactions, there are no studies that clearly demonstrate its effectiveness. In fact, in a study by Lee, 5 of 6 biphasic cases of anaphylaxis received corticosteroids initially at time of presentation (2). Bronchodilators are effective for patients developing wheezing and bronchospasm, although epinephrine alone may be sufficient.

Finally glucagon may be helpful in those patients on beta-blockers who develop anaphylaxis. There are no studies documenting effectiveness and only anecdotal accounts in the literature. The management of anaphylaxis also requires hospitalization or observation for 24 hours because of the possibility of biphasic anaphylaxis. All patients require at least observation since one cannot predict which patient will develop the biphasic response of anaphylaxis. However, if the parents are reliable observers and they are able to get to the hospital quickly, then the observation time in the emergency department can be shortened.

Physicians who identify a patient with a history of anaphylaxis should encourage their patient to obtain a Medic Alert bracelet or ID. The patient should be instructed on epinephrine use and dispensed an epinephrine syringe. Physicians should be responsible for demonstrating and training patients on the use of epinephrine syringes. However, considering the practical consideration that this epinephrine injector is not likely to be available (i.e., the patient won't have it) when their next reaction occurs, patients should also be taught the best means to obtain medical care depending on the severity of the reaction. Patients should also be prescribed an oral antihistamine, which should be taken immediately. Lastly, the management of anaphylaxis should be directed toward avoiding the offending agent and education of where the offending agent can be hidden (especially if it is a food item). For example, patients who are allergic to peanuts will probably react to foods cooked in peanut oil and patients with dairy product allergy may need to avoid butter and foods cooked with butter. This can be extremely challenging and almost impossible to avoid, especially at restaurants. An instruction to the waiter of "no peanut oil", will often translate to "use corn oil instead" to the cooks in the back. However, if the pan used had some peanut oil on it for the previous dish that was cooked, this may still be sufficient to cause a reaction in the patient. Allergy testing may be useful to determine the cause of the allergy and desensitization therapy may be useful for some types of allergies.

Urticaria, also commonly known as hives, are raised erythematous, circumscribed, pruritic lesions. Urticaria occurs from focal mast cell degranulation causing the release of histamine and other mediators. Individual lesions of urticaria generally do not remain in the same place for greater than 24 hours. Urticaria is divided into acute and chronic urticaria. Urticaria that lasts less than 6 weeks is acute and more than 6 weeks is chronic. Acute urticaria is more common in children and young adults, while the peak incidence of chronic urticaria is during the third and fourth decades (4).

Urticaria can occur from food allergies, collagen vascular disease, infections, environmental factors such as heat, cold or pressure, and medications. Despite an extensive workup, most cases of chronic urticaria is idiopathic. Urticaria is treated with antihistamines. In most instances, the urticaria should be largely resolved within several hours. H1 blockers, such as diphenhydramine or the newer non-drowsy antihistamines such as loratadine, are the standard therapy, but H2 blockers, such as ranitidine and cimetidine, have variable degrees of success so routine use is controversial (8). Avoidance of known triggers of urticaria is probably the most important aspect in chronic management.

Angioedema is a similar process that occurs in the deeper subcutaneous layers of the skin or mucus membranes, giving rise to nonpitting, stretched, colorless, well demarcated skin lesions. In contrast, urticaria lesions are typically raised, erythematous and pruritic. Characteristically, pruritus is absent in angioedema. There are fewer mast cells and sensory nerve endings in the deeper layers of skin involved. Most frequently, angioedema affects the scalp, lips, face, eyes, extremities and genitalia. Otherwise, angioedema is similar to urticaria with the main distinguishing feature of involvement into the dermis. Angioedema is treated similarly as urticaria.

Hereditary angioedema is an autosomal dominant disorder characterized by recurrent bouts of swelling typically affecting the face, extremities, respiratory and GI tract. This condition occurs because of the absence or abnormally functioning C1 esterase inhibitor. C1 esterase inhibitor prevents complement activation. If CI esterase is not functioning or absent, then the activation of the classical complement pathway could be unchecked. The disorder is usually self-limited, however, severe laryngeal edema or GI involvement may occur. Treatment involves the use of androgens, which causes the production of sufficient amount of C1 esterase inhibitor to prevent C1 activation.

Erythema multiforme may also resemble urticaria, especially in the early stages. However, erythema multiforme (EM) does not respond to antihistamines or corticosteroids. The lesions are varying in size and shape (multiformed) and some lesions have a target appearance with a rim of urticaria surrounding a central depression (target lesion). The most common presenting complaint is that of "hives" which has not responded to an antihistamine. Serum sickness may present a similar clinical picture. Joint swelling may accompany both conditions. These conditions generally resolve on their own within about 2 weeks. Withdrawing the allergic substance is a good idea, but it is usually not possible to determine what the inciting cause was. Group A beta hemolytic streptococci, herpes simplex and mycoplasma are known causes of EM, but there are numerous other causes as well. Stevens Johnson Syndrome is a severe form of EM (also known as EM major) which requires hospitalization. Treatment is supportive, but corticosteroids may be beneficial.

Questions

1. True/False: Anaphylaxis is well defined with its own clinical criteria.

2. What is the primary treatment of severe anaphylaxis and what is the appropriate dose?

3. What are some of the adjunctive therapies for anaphylaxis?

4. Two weeks following a viral illness, a teenage boy breaks out in an evolving rash that is remarkable for target lesions. What is the primary treatment?
   a. Epinephrine
   b. Glucagon
   c. Corticosteroids
   d. Antihistamines
   e. Symptomatic or supportive therapy depending on severity.

5. A girl is brought to her pediatrician by her mother because of recurrent bouts of non-pitting, non pruritic facial swelling that have occurred three times prior. Her father also has an history of recurrent facial swelling. What is the probably diagnosis?

a. Environmental allergen
b. Hereditary angioedema
c. Child abuse
d. Anaphylaxis
e. Urticaria

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Answers to questions

1. false
2. Epinephrine. Pediatric dosage for epinephrine is 0.01mg/kg up to a max dose of 0.5mg per dose or 0.5ml of 1:1000 SQ/IM Q15minutes for two doses and then Q4 hours as needed. The adult dosage is 0.2-0.5ml of a 1:1000 epinephrine solution.
3. Adjunctive therapies includes antihistamines, bronchodilators, and perhaps glucagon and corticosteroids.
4. e. This is erythema multiforme.
5. b

Chapter V.3. Food Allergies

Akaluck Thatayatikom, MD

Case 1

A 9 month old infant with severe eczematous rash is seen by his pediatrician. His mother reports that he has had this rash since 6 months of life when bottle feeding started. The skin rash did not respond to 1% hydrocortisone treatment and it has worsened in the past few weeks. On exam, he is noted to have generalized dry skin with subacute eczematous lesions on both cheeks and the extensor surfaces of his extremities without other abnormal findings. A diagnosis of cow's milk allergy is suspected which is confirmed by a highly positive CAP-RAST test for milk specific IgE antibody. He is successfully treated with 1% hydrocortisone cream, daily cetirizine (antihistamine), avoidance of cow's milk and dairy products, and a trial of soy milk formula feeding. His skin rash is controlled well within 2 weeks and this totally disappears after 1 year of age. At 3 years of age, cow's milk is accidentally given to him, however, no skin rash or other reaction is noticed. A cow's milk challenge is given to him in the physician's office and no reaction is noted. His cow's milk allergy has spontaneously resolved and he has no further problems with milk or dairy products.

Case 2

A 3 year old girl is brought to a pediatrician's office immediately since she develops her second episode of hives on her face and torso with dry coughing after eating peanut butter. Exam findings reveal normal vital signs, generalized expiratory wheezing and generalized urticaria. The symptoms respond well to diphenhydramine, subcutaneous epinephrine and an albuterol nebulizer treatment. Subsequently, she is evaluated by an allergist for possible peanut allergy. Her skin test demonstrates a strongly positive skin test (2 cm) and a CAP-RAST test shows a high level of peanut-specific IgE. Peanut avoidance is recommended. Her parents are given instructions on antihistamine and EpiPen use. In pre-school, she develops difficulty breathing and urticaria after eating a cookie given to her by another child. An ambulance is called and she is treated in an emergency department. At age 10, while on a school field trip, she develops urticaria, wheezing and she passes out after eating chili for lunch. An ambulance is called and she is treated with IV epinephrine, diphenhydramine, cimetidine and methylprednisolone for anaphylactic shock.

Case 3

A 16 year old female with seasonal allergic rhinitis is referred to see an allergist for evaluation of recurrent itching and swelling of her lips and tongue after eating bananas. The symptoms develop immediately after eating bananas and spontaneously resolve in 45 minutes. There is no history of sore throat, breathing difficulty, wheezing, GI symptoms, or skin rash. Physical examination at the visit are essentially normal. A skin test with a commercial extract yields a negative result; however, a skin test with fresh banana gives a positive result which confirms a diagnosis of oral allergy syndrome.

Case 4

An 11 month old boy develops a rash around his mouth after eating eggs. He is treated with hydrocortisone cream. He is taken to his physician and his parents ask if he might be allergic to eggs. A RAST test for eggs is ordered and the result is 1+ (very low). His

parents are informed that he is not allergic to eggs. His parents feed him some scrambled eggs two days later and he immediately develops hives and wheezing. He is treated with diphenhydramine, subcutaneous epinephrine and albuterol in an emergency department, where his parents are informed that he is probably allergic to eggs.

The four case scenarios illustrate common presentations, diagnostic work up approaches and management of food allergies. Food allergies are an increasing problem in westernized countries. Although an unpleasant reaction to food is often thought to be a food allergic reaction, only 8% of children under 3 years of age and roughly 2% of the adult population are affected by food allergies, which are mediated by an allergic/immune mechanism (e.g., IgE mediated). An adverse food reaction is a general term for a clinically abnormal response to an ingested food or food additive. Adverse food reactions may be caused by food hypersensitivity (allergy) or food intolerance. Food intolerance is a descriptive term of an abnormal physiologic response to an ingested food or food additive. The response is not immunologic in nature and it may be caused by many factors such as a toxic contaminant (such as histamine in scombroid fish poisoning or toxins secreted by Salmonella or Shigella), pharmacologic properties of the food (such as caffeine in coffee or tyramine in aged cheese) and idiosyncratic responses or host factors (such as lactase deficiency).

Food allergy, with acute onset of symptoms after ingestion, is IgE-dependent and potentially involves 4 major target organs: skin, GI, respiratory tract and cardiovascular systems. Acute urticaria and angioedema are the most common food allergic reactions, but the reaction may be a severe, life threatening event, such as anaphylactic shock. In fact, food allergies account for a large proportion of anaphylaxis cases in the United States. Other forms of acute presentations include: oral allergy syndrome, immediate gastrointestinal reaction (nausea, emesis, and diarrhea), anaphylaxis, rhinitis, asthma, and exercise-induced anaphylaxis. Delayed onset of food allergy symptoms includes atopic dermatitis, eosinophilic gastroenteropathies, dietary protein enterocolitis, dietary protein proctitis, dietary protein enteropathy, celiac disease and dermatitis herpetiformis. This chapter will focus on the IgE mediated food allergies.

Atopic dermatitis is a mixed IgE and cell mediated disease. There is substantial evidence indicating that food allergies cause many cases of atopic dermatitis in children, although food allergy is rarely a trigger of atopic dermatitis in adults. In a study, food allergies were found in 35% of children with moderate-severe atopic dermatitis (4). The skin lesions are generally provoked by an oral food challenge and are resolved by avoidance of the causal foods.

The pattern of food allergy in children is somewhat different from that in adults. The most common foods that cause problems in children are eggs, milk, peanut, soy, wheat, and fish. Most children will outgrow food allergy for eggs, milk or soy by age 4. In contrast, food allergies for shellfish (shrimp, crayfish, lobster, and crab), fish, peanuts and tree nuts are usually life-long.

An association of food allergy and latex allergy has been reported and confirmed. Approximately 30-50% of individuals who are allergic to natural rubber latex show an associated hypersensitivity to some fruits and vegetables (known as latex-fruit syndrome) such as avocados, bananas, chestnuts, kiwi, peaches, tomatoes, potatoes and bell peppers. Individuals who are allergic to pollens may produce specific IgE antibodies directed to homologous allergens of both pollens and fresh fruits/vegetables such as: 1) birch pollen with apples, peaches, pears, almonds, hazelnuts, potatoes and carrots. 2) ragweed pollen with melons and bananas. 3) mug wort pollen with celery and carrots. 4) grass pollen with tomatoes. This cross reactivity accounts for oral allergy syndrome in individuals with seasonal allergic rhinitis. The classic presentation of oral allergy syndrome is an acute episode of swelling, itching, tingling sensation, angioedema of lips or palate and erythematous mucosa localized only in the oral cavity after eating certain fresh fruits and/or vegetables (such as bananas, apples, peaches, carrots, melons, tomatoes) but not cooked fruits or vegetables since the allergens for oral allergy syndrome are heat labile.

In general, individuals do not develop clinical symptoms after being exposed to food allergens in the GI tract since the mucosal immune system and local GI factors (including intestinal epithelial cells, dendritic cells, T cells, mediators and gut flora) induce a state of unresponsiveness known as oral intolerance. Food allergy develops in genetically predisposed persons when oral intolerance fails to develop properly. In infants, the developmental immaturity of various components of the gut barrier and immune system increases the risk of developing food allergies during the first few years of life. The maturation of the gut with reduced systemic absorption and maturation of immune responses are thought to be the mechanism explaining why children outgrow food allergies or develop tolerance. Acute IgE-mediated reactions develop when food specific IgE antibodies residing on mast cells and basophils, bind circulating food allergens and activate the cells to release a number of potent mediators and cytokines. The pathogenesis of cell-mediated food allergy or delayed onset types remains unclear.

The diagnostic approach begins with the medical history and physical examination, followed by appropriate diagnostic tests. The goal is to determine whether the patient is likely to have experienced an adverse reaction to food involving an immunologic (allergic) mechanism. One should obtain information on: 1) the suspected food, 2) the quantity of the ingested food, 3) the time between ingestion and development of the symptoms, 4) description of the symptoms, 5) whether similar symptoms developed on other occasions when the food was eaten, 6) whether other factors (such as exercise) are necessary to provoke the reaction, and 7) the time since the last reaction. If an allergic reaction is suspected, it is essential to categorize reactions mechanistically (i.e., IgE mediated or non-IgE mediated) because subsequent diagnostic tests depend on the suspected mechanism. Most of the histories are useful and reliable only when the reactions are acute in onset such as with acute urticaria or anaphylaxis. In the case of delayed onset of symptoms such as atopic dermatitis, the history is often unreliable in implicating the offending allergens.

There are three methods to more definitely confirm or rule out IgE mediated food allergies: 1) Skin testing, 2) RAST, and 3) Oral challenge. Skin prick testing is done by pricking the skin with commercially available allergen extract solutions. Skin testing is generally done by allergists (i.e., not primary care physicians). A positive test identifies food specific IgE antibodies (suspected IgE mediated food allergy). A positive result yields a wheal (not erythema) of at least 3 mm in diameter larger than the negative control. A skin test that provokes a serious allergic reaction should also be considered to be diagnostic of a food allergy. There are some exceptions for interpretation of the results: 1) When testing a patient suspected of oral allergy syndrome, false negatives often occur if commercial food extracts are used for the skin test because these extracts are heat treated (rendering the allergen non-immunogenic, typical of oral allergy syndrome). However, by using a fresh fruit or vegetable for skin prick testing, a positive result may be confirmed as noted in the example described in case 3. 2) Children under one year of age may have IgE mediated food allergy without a positive skin test, and children under 2 years of age may have smaller wheals, possibly the result of a lack of skin reactivity. Negative skin prick test responses have excellent negative predictive values for excluding the presence of IgE mediated food allergy.

RAST (radioallergosorbent test) is an in vitro measurement of serum food specific IgE. The test is more available and practical for primary care physicians to evaluate food specific IgE antibodies. It should be noted that RAST tests are heterogenous yielding potentially unreliable results. CAP-RAST (the Pharmacia CAP system FEIA) is a newer generation of RAST which provides more reliable quantitative measurements of specific IgE levels. Table 1 is a recommended interpretation of food allergen-specific IgE levels (kUA/L) by CAP-RAST in the diagnosis of food allergies (5). For example, if a child's egg-specific IgE level is 7 or greater by CAP-RAST, there is a

greater than 95% likelihood that the child is truly allergic to eggs. In contrast, if the egg-specific IgE is less than 0.35 and there is no compelling history of egg allergy, there is a 95% chance that the child is not allergic to eggs. However, there is a 5% chance (1 in 20), that the child's CAP-RAST is falsely negative and that the child is allergic to eggs (as in case 4). If there is a strongly suggestive history of a food allergy, it should be noted that a low CAP-RAST can be misleading.

Table 1: CAP-RAST results

	95% NPV	95% PPV
Egg	0.35	7
Milk	0.35	15
Peanut	0.35	14
Fish	0.35	20
Soy	0.35	65
Wheat	0.35	80

If a CAP-RAST value falls somewhere between the 95% positive and negative predictive values (between the two values in the columns), it is uncertain whether a food allergy for that food exists. The patient will have to be referred to an allergist for skin testing, or an oral food challenge will have to be performed.

An oral food challenge is performed by feeding gradually increasing amounts of the suspected food under observation by a physician over hours or days. The double-blind, placebo controlled food challenge (DBPCFC), by giving increasing quantities of the suspected food allergen or placebo, either in opaque capsules or camouflaged in a liquid or semisolid vehicle, is considered the gold standard test of both IgE and non-IgE mediated food allergy. Elimination of the suspected food from the patient's diet for at least 7-14 days; withdrawal of potentially interfering medications (e.g., antihistamines); control of symptoms of chronic allergic disease (such as atopic dermatitis or asthma); administration of the challenge in a fasting state; use of fresh or dehydrated foods; and use of challenge vehicles that do not contain fat which can interfere with protein absorption, have been suggested to optimize the outcome. The absence of an allergic reaction after ingesting up to an equivalent of 10 grams of the dehydrated food essentially rules out a food allergy in that such a result has a high negative-predictive value. However, an average false-positive rate of 0.7% and false-negative rate of 3.2% for the DBPCFC were reported (7). Since the patient with IgE mediated food allergy may develop severe reactions to the challenge, the test should be performed by a well-trained physician in a facility capable of close monitoring, which is well equipped with drugs, supplies and equipment for resuscitation. The contraindication for such a test is recent anaphylaxis. An alternative to the DBPCFC,is a supervised open (unblinded) food challenge to confirm the safety of eating the particular food. This is recommended for a patient with a low likelihood of food allergy based on a low CAP-RAST result or an individual with a negative DBPCFC result.

A differential diagnosis of food allergies first aims to distinguish food allergies from food intolerance or other illnesses. Food poisoning is a possibility when food is contaminated by microorganisms and their products (such as toxins). Lactase deficiency, resulting in lactose intolerance, in children and adults, is a common food intolerance that is often confused with food allergy. There are also natural substances, such as histamine in cheese, wines and certain kinds of fish, that can occur in foods and stimulate a reaction similar to an allergic reaction. If someone eats one of these foods with a high level of histamine, that person may have a reaction similar to an allergic reaction to food. This reaction is called histamine toxicity, and it is often responsive to antihistamines. Reactions to MSG (monosodium glutamate) are not due to allergy mechanisms since MSG contains sodium and glutamate, both of which are normally present in the body. Excess amounts of consumed MSG are metabolized to neurotransmitters which may cause a reaction to MSG (Chinese restaurant syndrome) which is not allergic in nature.

The primary treatment for a child with a food allergy is to remove the offending antigen from the diet. In exclusively breast fed infants, a strict elimination of the causal protein from the diet of the lactating mother should be tried. Over time, many children who have food allergy (such as egg or milk) will develop tolerance to the food, making cautious, periodic attempts to introduce the offending food possible. An elimination diet can often be successful in children who have a single food allergy. However, dietary modification and nutritional counseling may be necessary for children who have multiple food allergies to identify hidden ingredients in processed foods and cross-reacting foods (e.g., peanuts, legumes). Aggressive restriction of allergenic foods may compromise the nutritional adequacy of the diet and interfere with the normal growth of the child. Patients and their families should be educated to avoid accidentally ingesting food allergens (e.g., by reading food labels), to recognize early symptoms of an allergic reaction, and to initiate early management of an anaphylactic reaction.

Many foods are ubiquitous in the environment and are often hidden in foods. Some helpful information can be obtained from www.foodallergy.org or www.anaphylaxis.org.uk. For example, a person eating peanuts may aerosolize sufficient quantities of peanuts to cause a nearby peanut allergic patient to react. Young children may share foods. Adults (other than parents) who serve food or supervise children (e.g., teachers, pre-school aids) are often not familiar with hidden foods in labels or they are not familiar with simple precautions. For example, peanuts are found in chili and scooping ice cream at a party may contain microcontamination with nuts if nuts are used in the ice cream of other children.

Just as an example, patients who are allergic to peanuts must learn to avoid peanut oil (Asian cooking), almond chunks (may actually be peanuts), baked goods, sauces (Chinese hot sauce, barbecue sauce, etc.), gravy, egg rolls (glue for edges), enchilada sauce, chili and other substances as well. Patients who are allergic to tree nuts (i.e., other nuts) must learn to avoid salad dressings, dessert toppings, sauces, exotic nut oils, pie crusts (almonds, macadamia nuts), ice cream toppings, cookies, almond extract, etc. Patients who are allergic to eggs must learn to avoid albumin, lysozyme, ovalbumin, egg substitutes (low cholesterol only), pastry, sauces, salad dressings, some shampoos, pet foods, influenza vaccine, cosmetics, fresh pasta, etc. Patients who are allergic to milk are usually allergic to the whey or casein protein in milk so they must learn to avoid whey, casein, ghee, nougat, rennet, caramel color, "natural flavors", canned tuna, hot dogs, imitation butter flavor, non-dairy whipped cream, non-dairy coffee whitener, imitation cheese, calcium caseinate, etc. Patients who are allergic to wheat must learn to avoid cracker meal, semolina, spelt, couscous, cornstarch, bulgar, farina (Cream of Wheat), etc. Patients who are allergic to fish must learn to avoid imitation crab, Worcestershire sauce (anchovy), Caesar salad (anchovy), many Asian foods (fish sauce), etc.

The above list is already difficult. Many pet foods contain nuts, which could be aerosolized when scooping this out for the pet dog. Facial scrubs may contain pulverized walnut shells. "Bean bag" furniture may contain walnut shells. Egg substitutes still contain eggs (with a reduced cholesterol formulation). "Non-dairy" products may still contain whey and casein.

Restaurants present a serious risk for patients with food allergies. When a cook is told to avoid a certain food, any pans, pots, woks, griddle surfaces or cooking utensils must not be exposed to any of these substances. For example, if a cook is attempting to avoid eggs, dairy products and peanuts, then the cooking surfaces and utensils must have no eggs, no butter and no peanut oil. If eggs were cooked on the griddle 30 minutes ago and the griddle was cleaned several times since, there may still be microscopic amounts of egg remaining. Similarly, cooking with butter or peanut oil is likely to leave microscopic residues on utensils or cooking surfaces, which may be sufficient to cause an allergic reaction.

An antihistamine is sometimes the only medication needed to reduce the itching and rash. In an acute event of anaphylaxis, immediate resuscitation is required. Epinephrine (0.01 ml/kg of the 1:1000 dilution given IM or subcutaneously) is often required for more severe allergic reactions. The term "anaphylaxis" is vague, but it implies a severe allergic reaction. Anaphylactic shock with associated vasodilation and hypotension, generally requires an IV epinephrine infusion with fluid replacement, in addition to preliminary IM or subcutaneous epinephrine. Having medical alert bracelets, carrying epinephrine for self injection and antihistamines available at home and school are strongly recommended for patients who have experienced a severe food allergy reaction. Some food allergies are more serious than others. On average, peanut allergies are the most serious, thus early epinephrine treatment should be considered even if a severe allergic reaction has not yet been encountered. Skin care with topical corticosteroid therapy and food avoidance is advised in food allergy induced atopic dermatitis. Immunotherapy by injection or sublingual administration of offending antigens has not proven to be effective in the management of patients who have food allergy. A new anti-IgE therapy (TNX-901, a humanized IgG1 monoclonal antibody against IgE) may alleviate some severe allergic reactions of peanut allergy (8).

There is some potential for prevention. Breastfeeding should be encouraged for all infants for the first 4-6 months of life. Breastfeeding mothers should avoid potentially allergic foods. Breastfeeding and the late introduction of solid foods (beyond the 5th month of life) is associated with a reduced risk of food allergy and other atopic diseases in early childhood. In formula fed infants with a documented hereditary atopy risk (affected parent or sibling), the exclusive feeding of a formula with a confirmed reduced allergenicity (protein hydrolysate formulas such as Nutramigen, Pregestimil and Alimentum) is recommended because it can reduce the incidence of adverse reactions to food, especially to cow's milk protein. There is no conclusive evidence to support the use of formulas with reduced allergenicity for preventive purposes in healthy infants without a family history of allergic disease. Preventive dietary restrictions after the age of 4-6 months are not scientifically documented (9).

Questions

1. Which one is likely to be a food allergic reaction in a teenager?
    a. Recurrent dizziness after eating Chinese foods.
    b. Recurrent tingling sensation in the mouth after eating a piece of apple.
    c. Recurrent palpitations after drinking a cup of coffee.
    d. Recurrent diarrhea after drinking a glass of milk.
    e. Recurrent facial redness (flushing) after drinking a glass of wine.

2. Which one of the following is an IgE mediated food allergy?
    a. Oral allergy syndrome
    b. Eosinophilic gastroenteropathies
    c. Dietary protein enterocolitis
    d. Celiac disease
    e. Dermatitis herpetiformis

3. Which one is the common natural course of cow's milk allergy in children?
    a. spontaneously resolves by age 4.
    b. spontaneously resolves by age 10.
    c. persists without changing severity.
    d. increases severity through their lives.
    e. is an unpredictable pattern.

4. Which one is the least common food allergy in children?
    a. Egg
    b. Peanut
    c. Soy
    d. Wheat
    e. Shrimp

5. Which food/fruit potentially causes an allergic reaction in a latex allergy individual?
    a. Banana
    b. Kiwi
    c. Tomato
    d. Potato
    e. All of the above

6. Which of the following are considered safe for patients with peanut allergy?
    a. Chinese and Southeast Asian foods
    b. Ice cream
    c. Dry pet food
    d. Chili
    e. Pastry
    f. None of the above

7. Which of the following are considered safe for patients with milk protein allergy?
   a. Lactose
   b. Non-dairy creamer
   c. Canned tuna
   d. Soy infant formula
   e. Hot dogs
   f. Casein

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Answers to questions

1.b. Tingling in the mouth after eating fruits suggests the possibility of an oral allergy syndrome. Dizziness after eating Chinese food is more likely due to an adverse non-allergic reaction to MSG. Facial redness after drinking a glass a wine may be due to tyramine.

2.a

3.a

4.e

5.e

6.f. Chinese and southeast Asian foods are frequently cooked with peanut oil. None of the above are safe. Ice cream is potentially contaminated by nuts since nuts are frequently served with ice cream or mixed with ice cream. Dry pet food and chili frequently contain peanuts. Pastry may contain peanuts even if they are called other types of nuts such as almonds.

7.a. Lactose is merely a disaccharide. Lactose by itself is not part of milk protein. However, if the source of lactose is a dairy product, then this dairy produce should be avoided. All of the other products including "non-dairy" creamers and canned tuna may contain milk or milk products.

Chapter V.4. Corticosteroids
M. Scott Hickman, MD

This is a 15 year old male with a PMH of steroid-dependent asthma who presents with a chief complaint of "always feeling tired and weak". Since the age of 7 he has taken inhaled bronchodilators, and for the last 4 years has used high doses of inhaled steroids. During the last 10 months, he required hospitalized twice for status asthmaticus, during which he was given IV and oral corticosteroid bursts. In addition, he has been taking daily oral steroids for the last 5 months. Review of symptoms is significant for a weight gain of 15 kg in the last 3 months, an increased incidence of recent "colds", and the observation by his mother that he seems not to be growing as quickly as his siblings did at this age. His mother also wants to know why, if her son is getting "steroids", he looks as he does rather than "all the athletes on TV who are using steroids".

Exam: VS T 37.3, P 88, RR 14, BP 145/98. Height is at the 10% percentile, and weight in the 50% percentile. He appears tired but in NAD. His visual fields are full. He has severe acne, truncal obesity and a "moon facies". His extremities show several small bruises, muscle wasting with 4/5 weakness, but no areas of hyperpigmentation were seen. There are two areas of poorly healing wounds on his left arm from a fall 3 weeks ago.

Labs: CBC of 14,000 with 1% eosinophils, 2% monocytes, 68% neutrophils, and 29% lymphocytes. Sodium 149, potassium 3.3, chloride 96, bicarbonate 28.5, glucose 110. Cortisol levels were slightly elevated with no diurnal variation.

Given the patient's history, the diagnosis of iatrogenic Cushing's syndrome is made. The patient is weaned off corticosteroid treatment over a period of 5 weeks. His Cushingoid features resolve and his height approaches the 40th percentile. An ophthalmology referral for a subsequent decrease in his vision identifies posterior subcapsular cataracts from his corticosteroid treatment, which are stable but do not resolve.

Corticosteroids are four-ringed steroid hormones produced by the adrenal cortex, with their common biochemical precursor being cholesterol. The corticosteroids are comprised of two major physiological groups: the glucocorticoids and the mineralocorticoids. However, the term "corticosteroids" is generally used to refer to glucocorticoids.

Mineralocorticoids, mainly aldosterone, influence electrolyte balance, and by consequence, intravascular volume and blood pressure. Glucocorticoids are named for their effect on carbohydrate metabolism, but they also have many other effects. One of their most important uses clinically is their complex effect on the immune system. Cortisol is the main physiologic glucocorticoid. Cortisol is called hydrocortisone when it is used pharmacologically. Androgens of the adrenal cortex affect the growth spurt seen in childhood and are responsible for secondary sexual characteristics. It is important to remember that these compounds are chemically similar, and there are clinically important areas of overlap seen in the effects of corticosteroids among these three groups; i.e., some glucocorticoids will have some mineralocorticoid effects, and vice versa.

The adrenal cortex has three layers (GFR): zona glomerulosa, zona fasciculata, zona reticularis, which are responsible for mineralocorticoids, cortisol, and androgenic steroids (salt, sugar, sex), respectively. Cortisol is also produced to some degree in the zona reticularis. Adrenal function is covered in the chapter on adrenal disorders. This chapter will focus on glucocorticoid corticosteroids.

Once corticosteroids are released from the adrenal cortex or absorbed in the body, 90% are bound to plasma proteins, the main two being corticosteroid-binding globulin (CBG) and albumin (1). Once the glucocorticoid is freed from its binding in the plasma by albumin or CBG, it crosses into the cytoplasm by simple diffusion to bind to the glucocorticoid receptor. In the cytoplasm, a glucocorticoid receptor is found in its inactive form bound to various heat-shock proteins. The heat-shock proteins dissociate, and the glucocorticoid-receptor dimer enters the cell nucleus. Short DNA sequences, called glucocorticoid response elements, interact with the glucocorticoid-receptor complex, and this regulates gene transcription by RNA polymerase II and associated transcription factors. The mRNA that is produced is ultimately exported to the cytoplasm for protein production and the final cellular response. Enzyme activity increased by cortisol results in an increase in providing carbon precursors (transaminases, etc.), conversion of pyruvate to glycogen (pyruvate carboxylase, glycogen synthetase, etc.), release of glucose (glucose-6-phosphatase) and disposal of ammonia liberated from urea cycle amino acids (arginine synthetase, argininosuccinase, etc.) (2). This whole process may take several hours for a response to be seen after corticosteroids are given.

In regards to the immune system, cortisol decreases the availability of arachidonic acid, a precursor to many of the inflammatory immune mediators, such as leukotrienes, prostaglandins, and thromboxanes. Cortisol has these effects by inducing the synthesis of a phosphoprotein called lipocortin that inhibits the activity of phospholipase A2. This decreases the synthesis of phosphatidyl choline to arachidonic acid. In addition, cortisol decreases the expression of the gene for cyclooxygenase 2 (which is involved in the production of leukotrienes and thromboxanes) and nitric oxide synthase (that decreases the production of nitric oxide that limits vasodilatation) (2). Corticosteroids are metabolized by the liver and made water soluble so that they may be excreted by the kidneys (1).

The fetal adrenal cortex has two zones, an outer definitive zone that is mainly responsible for glucocorticoid and mineralocorticoid synthesis, and a fetal zone which makes androgenic precursors used by the placenta. At one year of age, the fetal zone has involuted completely, and the definitive zone enlarges. The zona glomerulosa and zona fasciculata are not fully differentiated until age 3, and the zona reticularis may not be fully formed until age 15. At birth, the adrenal glands weigh 8-9 grams, which is twice the size of adult adrenal glands (3). High levels of cortisol may be seen in the first few hours of life, due to the high stress of birth and possibly due to increased levels crossing the placenta. Cortisol changes the fetal digestive pattern to the digestive enzyme capacity of an adult, allowing the newborn to use disaccharides present in milk (2). Cortisol prepares the fetal lung for breathing air by accelerating the rate of alveolar development and thinning of lung septa, and increasing pulmonary surfactant production by increasing the activity of phosphatidyl acid phosphatase and choline phosphotransferase. Betamethasone (a corticosteroid) is given clinically to mothers in premature labor to accelerate fetal lung maturation to reduce the severity of neonatal respiratory distress syndrome. Case reports of newborns with cleft palate, neonatal cataracts, growth retardation, and adrenal suppression have been reported in maternal corticosteroid use (4).

The use of inhaled corticosteroids at recommended doses in childhood does not have a substantial measurable effect on bone mineral density, ocular toxicity, or suppression of the HPA (hypothalamic pituitary adrenal) axis in childhood (5). Studies of inhaled corticosteroids on vertical growth have produced conflicting results. Its effects from childhood to adulthood are not known with certainty (4).

The various steroid compounds have differences in their glucocorticoid and mineralocorticoid activity which are related to their chemical structures, altering their affinities for the mineralocorticoids and glucocorticoids receptors. These structural changes also affect metabolism of the hormones by the liver, fat, or other tissues, its solubility and binding to plasma proteins, its ability to be absorbed, and

its excretion. Clinically, these affect the potency and duration of the corticosteroid. For example, if a double bond is placed in the 1,2 position of ring A, then a four-fold increase in glucocorticoid activity is seen with slower metabolism (longer duration) compared to hydrocortisone. This is the case with prednisolone and prednisone. Another example is fluorination at the 9-alpha position on ring B. This increases activity with the glucocorticoid receptor 10-fold, but also increases the mineralocorticoid activity by 125-fold, allowing these to be used as mineralocorticoids at small doses but with little to no glucocorticoid activity at the small doses used. If substitutions are made at C16 on ring D with the 9-alpha fluoro derivatives, then these compounds have marked glucocorticoid activity and virtually no mineralocorticoid activity (triamcinolone, dexamethasone, betamethasone) (1). Cortisone and prednisone are synthetic corticosteroids that require enzymatic reduction by the liver before becoming biologically active. In cases of severe hepatic failure, hydrocortisone and prednisolone should be used, since they do not require this enzymatic activation.

Hydrocortisone, and its synthetic analogs, are effective when given by mouth. Esters of hydrocortisone are more water-soluble and can be given intravenously for quicker and higher concentrations in the body. Glucocorticoids applied topically over the skin can be absorbed systemically with effects on the HPA axis if administration is prolonged or when high potency corticosteroids are used topically over large areas of skin.

Besides being classified by their mineralocorticoid and glucocorticoid relative potencies, corticosteroids can be classified by their duration of action. Short-acting glucocorticoids include cortisol (hydrocortisone) and cortisone. Intermediate-duration glucocorticoids include prednisone, prednisolone, triamcinolone, and methylprednisolone. Long-acting glucocorticoids include dexamethasone and betamethasone. The latter have very high glucocorticoid potencies and very little mineralocorticoid activity.

The table below summarizes glucocorticoid potency and duration. Substitutions and dose equivalencies can be made based on these values.

Glucocorticoid potency equivalence (7):

	Glucocorticoid equivalent dose (mg)	Glucocorticoid potency	Mineralocorticoid potency	Plasma half-life (minutes)
Short-acting, low potency				
Cortisol	20	1	2	90
Cortisone	25	0.8	2	80-118
Intermediate-potency				
Prednisone	5	4	1	60
Prednisolone	5	4	1	115-200
Triamcinolone	4	5	0	30
Methylprednisolone	4	5	0	180
Long-acting, high potency				
Dexamethasone	0.5	25-50	0	200
Betamethasone	0.6	25-50	0	300

When used pharmacologically (i.e., higher than physiologic levels), glucocorticoids have profound effects on inflammation and the immune response of lymphocytes. These two processes are linked because both involve leukocyte function. Glucocorticoids, as mentioned above, inhibit phospholipase and cyclooxygenase, limiting the release and production of prostaglandins, thromboxanes, and leukotrienes by mast cells, basophils, and eosinophils. By inhibiting leukotrienes, neutrophil phagocytosis and bacterial function are decreased. Glucocorticoids decrease extravasation of leukocytes and also diminish the secretion of lipolytic and proteolytic enzymes, so that fibrosis is reduced (1). In this way, glucocorticoids can be clinically used to modify (suppress) the inflammatory response. These therapeutic effects have a physiologic basis. Many immune mediators, such as IL-1, IL-6 and TNF-alpha, stimulate the HPA axis during times of stress, increasing glucocorticoids and thus causing a decrease in the immune response.

Glucocorticoids are used in physiologic doses to treat adrenal insufficiency and in pharmacological doses to treat inflammatory and autoimmune conditions. Given that cortisol levels can rise 10-fold in times of stress, high-dose corticosteroids may have a beneficial physiologic effect on the immune system. If the many immune mediators are unopposed by corticosteroids in times of stress, decreased vascular tone and cardiovascular collapse can occur. This important physiologic immune-modulating effect protects the body from an unchecked and full-blown inflammatory response that can have life-threatening consequences (1). Continued use of pharmacological doses can have other adverse effects, such as increasing susceptibility to various bacterial, viral, and fungal infections, permitting their dissemination. Corticosteroid use is contraindicated in patients with tuberculosis, and they must be used with extreme caution with ophthalmic herpes simplex infections. Hypertension, electrolyte and fluid abnormalities, osteoporosis, fat redistribution, acne, hirsutism, and myopathy (among others) can all develop with pharmacologic does of corticosteroids, especially when used over a long period.

Giving a patient glucocorticoids, also affects the amount of different immune cells found in the peripheral blood. The leukocyte count shows a polymorphonuclear leukocytosis (increased WBC count due to increased neutrophils which can be greater than 11,000) with lymphopenia (B and T cells), basopenia, a decreased monocyte count, and eosinopenia in four to six hours after a single dose of hydrocortisone. Neutrophils are increased due to demargination from vascular walls and increased release from the bone marrow. Lymphocytes, basophils, monocytes, and eosinophils are redistributed away from the periphery (1). Glucocorticoids can be used to treat various lymphoid malignancies, either due to being directly toxic to these cells or by inducing apoptosis (programmed cell death).

The acquired or adaptive immune system involves two main parts, cellular immunity and humoral immunity. Cellular immunity is manifested by cytotoxic T cells and natural killer cells involved in protection against intracellular bacteria, protozoa, fungi, and certain viruses. Humoral immunity provides protection against parasites, extracellular bacteria, soluble toxins and allergens, and certain viruses. It involves the production of antibody by B cells. These two systems are controlled by different types of helper T cells. Th1 cells, upon stimulation by IL-12, IFN-delta (among others) from antigen presenting cells (APC), causes a cellular immune response. Th2 cells, upon stimulation by IL4, cause a humoral response. These two systems are related, and an increase in IL-12, will inhibit IL-4 production, shifting the immune response to a mainly Th1, and thus a cellular immune response. Physiologic levels of glucocorticoids cause an

increase in humoral immunity, and a decrease in cellular immunity. This effect is mainly due to a glucocorticoid-induced inhibition of IL-12 secretion by APC and IL-12 responsiveness in Th1 cells. This inhibition of IL-12 frees IL-4 to have a more unopposed effect, triggering an enhanced humoral response (6).

Clinically, this decrease in cellular immunity has many important effects. Stress, and the subsequent physiologic increase in glucocorticoids and the Th2 shift, alters an individual's response to infection and autoimmune diseases. Cellular immunity is important in mycobacterial infections and HIV, correlating with the observation that these two diseases may be accelerated with stress and an increase in cortisol. Autoimmune diseases, although extremely complex in their pathophysiological mechanisms, can be thought of as involving mainly Th1 and Th2 mechanisms. Rheumatoid arthritis, multiple sclerosis, type I diabetes, and Crohn's disease are thought to be due to a hyperresponsive Th1 response, with excess IL-12 and TNF-alpha production. Women in their third trimester of pregnancy have increased levels of cortisol, which favors a Th2 response, and a expected remission of these diseases are seen during this time of pregnancy. In addition, decreased stress in the postpartum period or the stopping of glucocorticoid therapy can cause a worsening of these conditions. Th2 driven diseases, such as systemic lupus erythematous, can become worse during stress and pregnancy, when cortisol causes an increased Th2 response (6).

Glucocorticoids induce gluconeogenesis and they have catabolic effects on the periphery which supplies the liver with the amino acids and glycerol needed for gluconeogenesis. Glucocorticoids also decrease glucose uptake in adipose tissue, most likely by moving glucose transporters from the plasma membrane to an intracellular location. This can be thought of as protecting glucose-dependent tissues such as the brain and the heart from starvation during stress. Thus, under prolonged high levels of glucocorticoids, lymphoid tissue, muscle, fat, bone, and skin undergo wasting. This can lead to Cushing's syndrome, with a redistribution of fat from the periphery to the back of the neck (buffalo hump), face (moon facies), and supraclavicular area with less fat in the periphery. One hypothesis to this redistribution is that adipose cells in the neck, face, and supraclavicular area are sensitive to insulin, so the glucocorticoid induced hypoglycemia leads to increased fat deposition in these areas. The peripheral tissues are less sensitive to insulin and respond mainly to the glucocorticoid-induced lipolysis.

Corticosteroids are required for permissive contraction of skeletal muscle. Patients with Addison's disease frequently have fatigue and weakness as symptoms, which may be partly due to vascular insufficiency. Chronic use of corticosteroids can cause skeletal muscle wasting, called steroid myopathy.

Corticosteroids can have direct effects on a patient's mood and behavior. Patient's with Addison's disease can show psychosis, apathy, depression, and irritability. Glucocorticoid administration can have a stimulatory affect, with mood elation, euphoria, insomnia, restlessness, and increased motor activity. These effects are thought to be due to corticosteroid’s involvement in the regulation of neuronal activity (neurosteroids).

The most dangerous and life threatening complication of stopping corticosteroid therapy is acute adrenal insufficiency due to the HPA axis being suppressed by exogenous corticosteroids, disabling its ability to endogenously produce corticosteroids in sufficient quantities. By withdrawing corticosteroids, the so-called corticosteroid withdrawal syndrome can lead to cardiovascular collapse due to the loss of cardiovascular tone, with hypotension, shock, and death. Other symptoms of this syndrome include malaise, anorexia, headache, lethargy, nausea, and fever. Hypoglycemia and hyponatremia may be present. This should be considered in patients who have been given supraphysiologic (i.e., pharmacologic) doses of corticosteroids (e.g., a course of prednisone) in the previous year. Patients taking glucocorticoid therapy for 7-10 days can safely be discontinued abruptly. Those on longer therapy need to be tapered, with a 25% reduction in the previous weekly level usually recommended, although patients need to be followed clinically for signs of withdrawal (3). Once a physiological dose is achieved (8-10 mg per square meter body surface area per day) and the patient is stable, the dosage can be decreased to 4-5 mg per square meter per day for 4-6 weeks to allow the adrenal axis to recover. Most patients recover their HPA axis within several weeks, although there is wide variation and some may take a year or longer to recover fully, especially in the physiological response of the HPA to stress. Stress doses of glucocorticoids, usually 3-10 times the physiological replacement, are recommended if a physiologically stressful event (such as surgery) is encountered, for patients receiving chronic or long-term glucocorticoid therapy or for those who have been recently withdrawn from corticosteroids. A further problem of withdrawal can be a flare-up of the disease for which the corticosteroids were originally given.

Other complications or corticosteroids include Cushing's syndrome, growth retardation, the development of posterior subcapsular cataract formation, and advanced bone necrosis. Complications are unlikely if given for less than 2 weeks with moderate doses. Most side-effects of corticosteroids resolve with the exception of the formation of cataracts, which are permanent.

Questions

1. Which of the following is not a corticosteroid:
    a. cortisol
    b. aldosterone
    c. adrenal androgens
    d. norepinephrine

2. Glucocorticoids that are intermediate-potency include
    a. prednisone
    b. prednisolone
    c. triamcinolone
    d. dexamethasone
    e. a, b, and c

3. Immune system cells that are increased in the peripheral circulation after corticosteroid administration are
    a. neutrophils
    b. eosinophils
    c. lymphocytes
    d. monocytes

4. Safely tapering steroids in patient taking oral steroids for more than 10 days involves
   a. stopping steroid administration all at once
   b. changing a long-acting glucocorticoid to a short-acting glucocorticoid
   c. reducing previous weekly levels 10% with no clinical follow-up needed
   d. reducing previous weekly levels 25% with clinical follow-up

5. Glucocorticoids induce a Th2 shift by
   a. decreasing IL-12 production by antigen presenting cells, which allows an increase in IL-4 effects and thus more humoral immunity
   b. increasing IL-12 production by antigen presenting cells, which allows for a decrease in IL-4 and thus more humoral immunity
   c. glucocorticoids induce a Th1 shift
   d. none of the above

6. Glucocorticoids do NOT reduce inflammation by
   a. inhibiting phospholipase and production of arachidonic acid
   b. inhibiting cyclooxygenase and production of prostaglandins and thromboxanes from arachidonic acid
   c. decreasing the levels of neutrophils in the peripheral blood
   d. inhibiting leukotriene action and thus neutrophil function
   e. decreasing production of nitric oxide by inhibiting nitric oxide synthase

7. A physician orders 40 mg of IV methylprednisolone for a 20 kg patient (2 mg/kg) with status asthmaticus. The hospital pharmacy notifies the physician that IV methylprednisolone is not currently available and is on back order. Utilizing corticosteroid potencies, which of the following are approximate glucocorticoid equivalents?
   a. Dexamethasone 4 mg (0.2 mg/kg)
   b. Hydrocortisone 200 mg (10 mg/kg)
   c. Prednisone 40 mg (2 mg/kg)
   d. Dexamethasone 400 mg (20 mg/kg)

8. Explain how corticosteroids could be beneficial in croup and status asthmaticus due to a viral pneumonia. In both instances, a viral infection is causing the problem. Since corticosteroids are potentially immunosuppressive agents, is there a net beneficial or detrimental effect?

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Answers to questions

1.d. Norepinephrine is a hormone of the adrenal medulla, not the adrenal cortex. Corticosteroids are by definition hormones of the adrenal cortex.

2.d. Dexamethasone is a high-potency, long-acting glucocorticoid. Prednisone, prednisolone, and triamcinolone are intermediate-potency glucocorticoids.

3.a. Eosinophils, lymphocytes, and monocytes are reduced in the peripheral circulation after corticosteroid administration. Although neutrophil numbers are increased, their bactericidal activity is decreased.

4.d. Safely tapering corticosteroids in a patient who has taken corticosteroids for more than 10 days, involves reducing the previous week's levels by 25%, and the patient should be monitored clinically for signs of corticosteroid withdrawal (malaise, anorexia, headache, lethargy, nausea, fever, loss of cardiovascular tone, with hypotension, shock, and death) and a worsening of the condition that the corticosteroids were originally given for.

5.a. Th1 cells are stimulated by IL-12 from APC to cause a cellular immune response. Th2 cells, upon stimulation by IL4, cause a humoral response. IL-12 will inhibit IL-4 production as well. Glucocorticoids cause a decrease in IL-12 secretion by APC and IL-12 responsiveness in Th1 cells. This inhibition of IL-12 frees IL-4 to have a more unopposed effect, triggering an enhanced humoral response.

6.c. Glucocorticoids inhibit production of arachidonic acid, prostaglandins, thromboxanes, leukotrienes, and nitric oxide, all of which are involved in the inflammatory response. Neutrophils are increased in the peripheral blood, not decreased.

7. a,b,c are correct. 0.2 mg/kg of dexamethasone would probably be the best answer, although its duration is longer than that of methylprednisolone. This should not be a problem for status asthmaticus. 10 mg/kg of hydrocortisone has equivalent glucocorticoid activity, but it has unnecessary mineralocorticoid activity. 2 mg/kg of prednisone is roughly the same as 2 mg/kg of methylprednisolone, but prednisone would have to be given orally since it cannot be given IV. 20 mg/kg of dexamethasone is clearly an overdose, which results from multiplying by 10 instead of dividing by 10. A good clue would be that dexamethasone comes in 10 mg vials. A 400 mg dose

would require 40 vials. This should clearly prompt questioning by pharmacy and nursing staff. Whenever a pediatric dose requires more than one vial, the dose should be questioned.

8. The symptoms of croup and status asthmaticus are largely due to the inflammatory response induced by the viral infection. The virus itself causes less of a problem compared to the body's inflammatory response. Corticosteroids suppress the inflammatory response resulting in less laryngeal and bronchial inflammation. It cannot be assumed that this is true for all viral infections. For example, in viral pharyngitis, the symptoms of a sore throat and nasal congestion may be suppressed with corticosteroids. However, it may cause more harm than good. In the case of croup and status asthmaticus, numerous studies have supported the net benefit of corticosteroids in these two conditions. In bacterial meningitis due to H. flu, a similar benefit has been demonstrated, but for bacterial meningitis due to other organisms and for viral meningitis, the benefit has not been clearly demonstrated.

Chapter V.5. Immune Deficiency
Akaluck Thatayatikom, MD

This is a 14 month old male infant who presents to the emergency department with a chief complaint of high fever and no response to antipyretic therapy. This illness started suddenly with the abrupt onset of fever early yesterday morning. He then developed a severe cough and increased work of breathing. No other symptoms are noted. The patient was born in a refugee camp and has lived in Florida and Texas before moving to Hawaii 3 months ago. The mother reports that he is frequently ill. No reports from Florida or Texas are available, but his mother reports he was also seen as an outpatient frequently and he was hospitalized at least once in Florida. He was hospitalized 2 months ago for pneumococcal pneumonia (right upper lobe consolidation and pneumococcal bacteremia).

Exam: VS T 40.3, P 145, R 55, BP 100/60, oxygen saturation 98%, weight 7 kg (<5th percentile). He is a listless, tired, and small for age. He is lying on the gurney, moving little and whimpering slightly to stimulation with tachypnea and chest retractions. His head is normocephalic, without signs of trauma. Both ear canals contain purulent drainage. Mouth exam is unremarkable. His heart is tachycardic with no murmurs heard. His chest shows mild retractions, tachypnea, dullness to percussion over the posterior upper chest, decreased breath sounds in the area of dullness with occasional fine crackles. His abdomen is scaphoid and soft, with active bowel sounds, no masses, and no hepatosplenomegaly. His extremities are slender and wasted with decreased muscle mass and strength. Neurological exam is normal.

Because of his poor general appearance, he is hospitalized for possible sepsis. He is treated with intravenous antibiotics and he improves slowly over one week. A blood culture is positive for pneumococcus. Because of his recurrent infections and the failure to meet normal growth expectations, an immunologic work up is done. He is found to have markedly elevated IgM, undetectable IgG and IgA with diminished total B lymphocytes (CD19). His clinical picture is consistent with hypogammaglobulinemia with high IgM or Hyper-IgM syndrome. A confirmed diagnosis shows a deficiency of CD40 ligands on T cells. He is placed on monthly IVIG replacement therapy with trimethoprim-sulfamethoxazole prophylaxis for Pneumocystis carinii pneumonia (PCP) and he begins to gain weight and he clears his ear infections.

Recurrent infections in children are one of the common problems encountered by physicians. The majority of these children have normal immune function. However, some patients have immune deficiencies and these patients are frequently not diagnosed. Therefore, physicians should be aware of recurrent infections caused by non-immunologic conditions (Table 1) and clinical clues suggestive of immunologic disorders (Table 2). Immune defects may be either primary (congenital) or secondary to certain diseases or agents (Table 3).

Table 1: Nonimmunologic Causes of Recurrent Infections

Abnormal mucous membranes and integuments: Burns, severe eczema, bullous diseases, ectodermal dysplasia, percutaneous catheters.

Obstruction of hollow viscus: Cystic fibrosis, inhaled foreign body, posterior urethral valves, ureteropelvic junction obstruction.

Foreign body: Ventriculoperitoneal shunt, prosthetic cardiac valves, orthopedic devices, catheters.

Vascular abnormalities: Large left to right intracardiac shunt, diabetes mellitus.

Congenital: Cysts and sinus tracts, tracheoesophageal fistula, abnormal ciliary function.

Neurologic: Incoordinate swallowing, recurrent aspiration, poor respiratory effort.

Metabolic disorders: Galactosemia, certain amino acid and organic acid disorders.

Secondary immunodeficiency: Malignancy, chemotherapy, chronic renal failure, protein losing enteropathy.

Table 2: Conditions suggestive of immune deficiency

>10 episodes acute otitis media per year (infants and children).

>2 episodes consolidated pneumonia per year.

>2 life-threatening infections per lifetime.

Two or more serious sinus infections within 1 year.

Unusual organisms.

Unusual response to organism.

Recurrent deep skin or organ abscesses.

Two or more deep-seated infections such as meningitis, osteomyelitis, cellulites or sepsis.

Persistent oral thrush or candida infection elsewhere on the skin, after age 1 year.

Recurrent autoimmune phenomena.

Dysmorphic features associated with recurrent infection.

Infections worsening chronic disorders (asthma or seizure).

Development of vaccine pathogen after vaccination (e.g., HiB infection despite previous HiB vaccine).

Family history of immunodeficiency or recurrent infection.

Table 3: Classification of Primary and Secondary Immunodeficiency Disorders

Primary Antibody Deficiency Diseases (50%):
- X-linked agammaglobulinemia.
- Hyper-IgM syndrome, autosomal recessive.
- Common variable immunodeficiency (CVID).
- IgA deficiency.
- Selective IgG subclass deficiencies.
- Specific antibody deficiency with normal immunoglobulins (SADNI).
- Transient hypogammaglobulinemia of infancy.

T-cell and Combined Immunodeficiency Diseases (30%):
- Severe combined immunodeficiency (SCID).
- X-linked Hyper-IgM syndrome.
- DiGeorge anomaly.
- Wiskott-Aldrich syndrome (WAS).
- Ataxia-telangiectasia (AT).
- Cartilage-hair hypoplasia.
- Chronic mucocutaneous candidiasis.
- X-linked Lymphoproliferative syndrome.

Phagocytic Disorders (18%) (described further in the chapter on neutrophil disorders):
- Chronic granulomatous disease (CGD).
- Leukocyte adhesion defect (LAD).
- Cyclic neutropenia.
- Chediak-Higashi syndrome.
- Myeloperoxidase deficiency.
- Shwachman syndrome.
- Kostmann's syndrome.

Complement Deficiency (2%):
- C1q, C1r, C2-C7, C8a, C8b, C9, C1 inhibitor.
- Factor I, H, D, Properdin.

Other well defined immunodeficiency:
- Hyper-IgE syndrome.
- Lymphoproliferative syndrome.

Immunodeficiency associated with other congenital conditions:
- Down syndrome
- Shwachman syndrome

Secondary Immunodeficiency:
- Malnutrition.
- Infection (congenital rubella, HIV infection, infectious mononucleosis and other such infections).
- Protein-losing enteropathy.
- Nephrosis.
- Sickle cell disease.
- Infiltrative diseases such as histiocytosis, leukemia.
- Metabolic problems such as diabetes mellitus, uremia, vitamin and mineral deficiency.
- Immunosuppressive medications.
- Splenectomy.
- Disruption of barrier protection (burns, severe eczema, catheters).

Over 70 primary immune deficiency diseases have been recognized. The antibody deficiencies constitute about 50% of all cases of primary immunodeficiencies. T cell deficiencies and combined immunodeficiencies are the second largest group, making up about 30%. Phagocytic defects and complement disorders make up about 18% and 2% of immunodeficiencies. Only the more common primary immune deficiency syndromes will be emphasized in this chapter. HIV infection is covered in a separate chapter.

1. Transient hypogammaglobulinemia in infancy (THI). THI is due to a normal variability of the developing immune system in infants with prolonged periods of physiologic hypogammaglobulinemia. All infants develops physiologic hypogammaglobulinemia at approximately 5-6 months of age. In these age groups, the serum Ig level reaches its lowest point (approximately 350mg/dl), and many normal infants begin to experience recurrent respiratory tract infections. The diagnosis of THI is based on low levels of IgG and normal levels of IgA with variable levels of IgM. The normal levels of IgA exclude other congenital hypogammaglobulinemia. Most children with THI are typically able to synthesize specific antibodies in response to immunizations. However, inadequate specific antibody responses do not exclude the diagnosis of THI, but should prompt further investigation for other forms of immunodeficiency. Most cases of THI will spontaneously resolve by 4 years of age.

2. X-linked agammaglobulinemia (XLA) is characterized by four findings: 1) Onset of recurrent bacterial infections in the first 5 years of life; 2) Serum IgG, IgM and IgA values that are at least 2SD below the normal for age; 3) Absent isohemagglutinins or poor response to vaccines; and 4) Less than 2% CD19+ B cells in the peripheral circulation. It should be noted that the variability of clinical and laboratory findings for XLA is exist. Some XLA cases have been undiagnosed and untreated for more than five decades. 10-20% of XLA have serum IgG values greater than 200mg/dl at the time of diagnosis. The most consistent findings in XLA are the marked reduction in the number of B cells in the peripheral circulation.

The primary defect in XLA is the failure of pre-B cells to differentiate into mature B lymphocytes due to a gene mutation of Bruton's tyrosine kinase (Btk) which plays a multifaceted role in signal transduction for normal B cell development. However, approximately 10% of boys with presumed XLA do not have the mutation in Btk and 10% of patients with the early onset of recurrent

infections, profound hypogammaglobulinemia and absent B cells, are girls. These observations suggest that there are autosomal recessive disorders clinically indistinguishable from XLA.

Intravenous immunoglobulin (IVIG) has been used as a mainstay therapy for XLA and other antibody deficiency disorders or combined immunodeficiency including autosomal recessive agammaglobulinemia, CVID, Hyper-IgM syndrome, SCID, WAS and AT. IVIG therapy may be beneficial for a selective antibody deficiency with IgG1 or IgG2 deficiency and significant recurrent infections. The usual dose of IVIG is 400 mg/kg every 4 weeks and then the dose should be adjusted based on the IgG level after 3-4 infusions (to keep IgG levels above 500mg/dl). Headache, fever, myalgia, chills, rigors, nausea and vomiting are common adverse reactions of IVIG infusion; however, aseptic meningitis has been reported.

3. Common variable immunodeficiency (CVID) is a heterogeneous syndrome, presenting with low IgG levels and no association with drugs or diseases known to cause secondary antibody deficiency. More than 95% of CVID clinically presents with recurrent sinopulmonary infections just like XLA or other hypogammaglobulinemia syndromes. The cause of CVID has not been identified yet. However the intrinsic defects of B cells, diminished T helper cells and dysregulation of cytokines have been described. Most of the patients usually do not become symptomatic until 15-35 years of age. CVID patients have an increased risk of developing autoimmune diseases, lymphatic and gastrointestinal malignancies, malabsorption and granulomatous inflammation.

The diagnosis of CVID is based on low IgG levels and poor specific antibody responses to immunizations without an identified cause of the hypogammaglobulinemia. IgM and IgA levels may present in significant amounts or absent. A patient with borderline immunoglobulin levels needs an evaluation of specific antibody responses with immunizations. T cell and B cell enumeration are usually normal; however, decreasing numbers of the cells have been occasionally seen. Some patients may have abnormal T cell function studies such as absent delayed hypersensitivity or depressed responses of mitogen stimulation. Treatment of CVID is identical to XLA. Frequent use of broad-spectrum antibiotics is required. The delayed diagnosis and treatment leads to chronic lung diseases such as bronchiectasis so periodic screening with chest x-rays, high resolution chest CT and pulmonary function tests are needed.

4. Hyper-IgM syndrome (HIM) is characterized by high levels of IgM with deficiency of IgG, IgA and poor specific antibody responses to immunizations. X-linked hyper-IgM syndrome is the commonest type which has a defect of the CD40 ligand (CD40L or CD154) gene of T cells. The interaction between CD40 on the B cells and CD40L on T cells is essential for the immunoglobulin class switching from IgM to IgG production, which explains why a deficiency in CD40L leads to hyper-IgM production with deficiency of IgG and IgA. HIM presents with recurrent sinopulmonary infections and Pneumocystis carinii pneumonia (PCP). There are associated abnormalities including neutropenia, hemolytic anemia and aplastic anemia. The unique susceptibility to opportunistic infections and neutropenia with high IgM levels distinguishes HIM from XLA or other hypogammaglobulinemias. Treatment of HIM is based on regular administration of IVIG and use of trimethoprim-sulfamethoxazole to prevent PCP. IVIG not only reduces the severity and frequency of infections, but also diminishes IgM levels and neutropenia. G-CSF (granulocyte colony stimulating factor) may be given for severe neutropenia. Recently stem cell transplantation has been performed successfully. The long term prognosis of HIM appears to be worse than in other forms of congenital hypogammaglobulinemia. Pneumocystis carinii infection has an important impact on morbidity and mortality during the first years of life, whereas liver disease mainly contributes to late mortality.

5. Selective IgA deficiency is the most common primary immunodeficiency disorder with the prevalence between 1 in 400 to 1 in 800. Although many patients are asymptomatic, IgA deficiency predisposes to respiratory, GI and urogenital tract infections, autoimmune diseases, sprue-like syndrome, malignancy, allergy and anaphylaxis reactions to blood products. Moreover, the progression of selective IgA deficiency to CVID or IgG2 subclass deficiency has been reported. The cause of the disease has not been known. Some infectious agents and drugs such as congenital rubella, EBV infection or phenytoin, may cause low IgA levels. The physiologic lag in serum IgA may delay the diagnosis until after the age of 2. The diagnosis can be made if a patient presents with IgA levels less than 7 mg/dL with no other evidence of any immune defects. Unlike XLA, HIM or CVID, selective IgA deficiency has a normal IgM and IgG response to pathogens and vaccines, therefore the routine schedule of immunization is suggested. IVIG replacement is not indicated. Aggressive treatment with broad spectrum antibiotics is recommended for recurrent sinopulmonary infections to avoid permanent pulmonary complications. Some selective IgA deficiency patients may develop antibody to IgA, in which case, there is a risk of anaphylaxis with blood product transfusions.

6. Selective IgG subclass deficiencies are generally defined as a serum IgG subclass concentration that is at least 2 standard deviations below the normal for age. There are four subclasses of human IgG, designated IgG1, IgG2, IgG3 and IgG4. Approximately 67% of serum IgG is IgG1, 20-25% is IgG2, 5-10% is IgG3 and 5% is IgG4. The concentrations of IgG subclasses are physiologically varied with age; IgG1 reaches adult levels by 1 to 4 years of age, whereas IgG2 level normally begins to rise later in childhood compared to other subclasses. The subclass deficiency has been reported in patients with recurrent infections, despite normal total IgG serum or with an associated deficiency of IgA and IgM deficiency.

The diagnosis and its implication have long been problematic since there are insufficient normative data for very young children and major technical problems of measurement of IgG subclass. Additionally, normal healthy children with low IgG2 subclass levels and normal responses to polysaccharide antigens as well as completely asymptomatic individuals with lacking IgG1, IgG2, IgG4 have been reported. A low value of IgG2 in a child may be a temporary finding which normalizes in adulthood. Approximately 10% of males and 1% of females have IgG4 deficiency without significant infections. IgG3 levels may be low with an active infection because it has the shortest half life and the greatest susceptibility to proteolytic degradation. Therefore, IgG subclass measurements are not routinely recommended and treatment with IVIG should be reserved for the patients who have been clearly demonstrated to have impaired responses to both protein and polysaccharide antigens to which they have been immunized.

7. Severe combined immune deficiency (SCID) is a life-threatening syndrome of recurrent infections, oral candidiasis, persistent diarrhea, dermatitis, graft versus host disease after blood transfusion and failure to thrive caused by a number of molecular defects that lead to severe compromise in T cell function with or without B cell dysfunctions. The defects in SCID block the differentiation and proliferation of T cells and in some types, of B cells and natural killer (NK) cells. Immunoglobulin and antibody production are severely impaired even when mature B cells are present. NK cells, a component of innate immunity, are variably affected. The majority of the patients present by age 3 months with unusually severe and frequent common infections such as bacterial otitis media and pneumonia or opportunistic infections including Pneumocystis carinii, and cryptosporidiosis. Viral infections such as herpes simplex, RSV, rotavirus, adenovirus, enterovirus, EBV, CMV are also commonly seen.

The most common defect of SCID is X-linked SCID (XL-SCID), accounting for 50-60% of cases. Adenosine deaminase (ADA) deficiency, accounting for 15% of SCID, is the second common defect. Other defects are purine nucleoside phosphorylase (PNP) deficiencies, IL-7 receptor alpha chain deficiency, recombination activation gene-1 and gene-2 (RAG1, RAG2) deficiency, CD45 deficiency, CD3 deficiency, MHC class I and II deficiency.

SCID is typically diagnosed by clinical features: absence of lymph nodes and tonsils, lymphopenia, absence of a thymic shadow on chest x-ray, abnormal T, B, NK cell enumeration with flow cytometric analysis, abnormal in vivo T cell function studies with skin tests of delayed skin hypersensitivity to tetanus, candida, diphtheria and in vitro lymphocyte function studies by measuring response to phytohemagglutinin (PHA), concanavalin A, pokeweed mitogen, phorbol myristate acetate (PMA) and ionomycin, tetanus and candida.

Skin testing for delayed hypersensitivity (which tests type IV cellular immunity function) is a basic way of testing T cell function. Antigens such as tetanus, candida, trichophyton, and mumps are frequently used because nearly everyone should be positive to all of these; however, occasionally normal young children may have a negative response. A positive response to these intradermal antigens indicates intact T cell function. If no response results from all these antigens, the patient may be "anergic". Thus, this panel of antigens is known as an "anergy panel".

Bone marrow or other stem cell reconstitution is a first-line, specific therapy for almost all forms of SCID. ADA deficiency has specific therapy as an alternative to the transplantation. Polyethylene glycol-treated (PEG) ADA replacement may be administered with improvement but not complete reconstitution of immune function. Currently gene therapy is successful for XL-SCID. Prophylactic antibiotics, IVIG replacement, meticulous skin and mucosal hygienic care, avoidance of exposure to infectious agents, and irradiation of all blood products prior to transfusion are recommended while awaiting stem cell reconstitution. Many patients with SCID are fully reconstituted without complications with bone marrow and other stem cell reconstitution techniques. Patients who are well nourished, uninfected and younger than 6 months prior to transplantation have the best outcomes. Without stem cell reconstitution, it is rare for a patient with SCID to survive.

8. Complement deficiency: Complement proteins are a key component of the innate immune system due to their function of direct lysis of their targets and being an opsonin. Most of the complement deficiency diseases are inherited in an autosomal recessive mode except C1 inhibitor deficiency (autosomal dominant) and properdin deficiency (X-linked). C2 deficiency is the most common defect; however, 50% of individuals with C2 deficiency are asymptomatic. Patients with C1, C4, C2 and C3 deficiencies have a higher incidence of autoimmune diseases such as SLE and encapsulated bacteria infections. Patients with absent factor H and factor I will have excessive consumption of C3; therefore, those patients will have similar infections as those with C3 deficiency states. The most commonly performed test for evaluation of functional complement activity is the CH50 test. APH50 is a useful screening test for the alternative pathway. There is no specific treatment for complement deficiency, except a purified C1 inhibitor preparation for hereditary angioedema due to C1 inhibitor deficiency.

9. WAS is an X-linked recessive disease, caused by a defective gene encoding Wiskott-Aldrich syndrome protein (WASP), which is expressed only in lymphocytes and megakaryocytes. This protein is involved in the reorganization of the actin cytoskeleton in the cells. WAS has a classic presentation with eczema, microcytic thrombocytopenia and recurrent encapsulated infection in a young boy. The initial manifestations often present at birth and consist of petechiae, bruises, bleeding from circumcision or bloody stools. The diagnosis can be made based on the manifestations and immunologic findings including low IgM, high IgA and IgE, poor antibody responses to polysaccharide antigens, moderately reduced number of T cells and variable depression of in vitro T cell function studies. Treatment includes IVIG infusion, irradiated fresh platelet transfusions and splenectomy for bleeding tendency, prophylactic antibiotics after splenectomy, and bone marrow transplantation.

10. Ataxia-Telangiectasia (AT) is an autosomal recessive disorder characterized by sinopulmonary infections, telangiectasia, progressive ataxia and hypersensitivity to ionizing radiation. Immunologic studies reveal combine immunodeficiency consisting of selective IgA and IgG2 deficiency, cutaneous anergy and depression of in vitro T cell function study. Supportive treatment is recommended. Other treatments which may be considered include IVIG and bone marrow transplantation.

11. Hyper-IgE syndrome is characterized by chronic pruritic dermatitis, recurrent staphylococcal infections (skin and respiratory tract), markedly elevated serum IgE, eosinophilia and coarse facial features. The diagnosis may be difficult since there is no clear definition of high IgE levels and IgE levels may fluctuate from time to time. In addition, a high IgE level with eosinophilia is commonly seen in severe atopic dermatitis. Therefore, recurrent staphylococcal infections involving the skin, lungs and joints with other features including a distinctive facial appearance, dental abnormalities and bone fractures are essential for the diagnosis. Treatment with good skin care and continuous antimicrobial therapy such as trimethoprim-sulfamethoxazole are necessary. No specific immunotherapeutic regimen has been successful. The role of IVIG therapy remains to be determined.

12. Chronic granulomatous disease (CGD) is a defect of phagocytic cells with dysfunction of the NADPH oxidase enzyme complex required for the production of reactive oxygen intermediates to destroy microbes. The defect leads to recurrent and uncontrolled catalase-positive organisms including S. aureus, E. coli, Serratia marcescens, Salmonella, Klebsiella spp, Clostridium difficile, Legionella bosmanii, Pseudomonas cepacia, Mycobacterium fortuitum, Chromobacterium, Aspergillus spp, Nocardia spp and Actinomyces spp. The most common infections are lymphadenitis, abscesses of the skin, and of the viscera such as liver. Granuloma formation occurs in CGD because the defect of the intracellular microcidal mechanism causes persistent antigen presentation and induces a sustained cell-mediated response by CD4 T cells, which recruit other inflammatory cells and set up a chronic local inflammation called a granuloma. The diagnosis of CGD can be ascertained by taking advantage of the metabolic defect in the phagocytic cells. A dye called nitro blue tetrazolium (NBT) is pale yellow and transparent. When it is reduced, it becomes insoluble and turns a deep purple color. In normal blood, the NBT is reduced to a dark purple or blue, easily seen in the phagocytic cells. In CGD blood, no dark purple or blue color is seen. Treatment includes short-term treatment of the infections, prophylactic trimethoprim-sulfa, recombinant human interferon-G (enhancing the production of reactive oxygen intermediates) and bone marrow transplantation. This condition is described in further detail in the chapter on neutrophil disorders.

13. Leukocyte adhesion molecule defect (LAD) syndromes are failures of innate host defenses against bacteria, fungi, and other microorganisms resulting from defective tethering, adhesion, and targeting of myeloid leukocytes (PMN, monocytes) to sites of microbial invasion. Killing of microbes is intact, but since the cells can not be mobilized to the point of inflammation and complement-mediated phagocytosis is impaired, the result is a lack of an inflammatory response. The hallmark of the disease is neutrophilia without PMNs in the infected tissue or pus. Histories of delayed separation of the umbilical cord, recurrent bacterial infections, necrotic skin lesions, severe gingivitis, periodontitis, and alveolar bone loss leading to early loss of deciduous and permanent teeth suggest the diagnosis. A definitive diagnosis with flow cytometric analysis reveals a decreased or absence of CD18 and its associated heterodimers: CD11a,CD11b and CD11c in LAD type I and absence of CD15s in LAD type II. Treatment includes continuous antimicrobial therapy, good oral hygiene, white blood cell transfusions and bone marrow transplantation.

Clinical Approach to Suspected Immunodeficiency

The history should include the onset and type of the infections, the frequency, chronicity, severity and the responses to the previous treatments. The associated conditions such as failure to thrive, autoimmune disease, congenital anomalies and family history of consanguinity, fetal wastage and early childhood deaths should be noted. Types of infections and presentations are helpful for differentiation of primary immune defects (Table IV).

Table IV: Typical Clinical Findings in Each Group of Primary Immunodeficiency

Antibody Deficiency Diseases:

Presentation after passively acquired maternal antibody wanes (6 months old).
Infection with encapsulated bacteria such as Haemophilus influenzae type B, pneumococcus, etc.
Recurrent sinopulmonary infection, otitis media.
Possible poor growth or failure to thrive.

T-Cell and Combined Immunodeficiency:

Presentation in early infancy.
Poor growth or failure to thrive.
Persistent oral thrush.
Opportunistic infection.

Phagocytic Defects:

Presentation in infancy or childhood.
Poor wound healing, delayed umbilical cord separation..
Gingivitis, abscesses, skin infection, including cellulitis and furunculosis.

Complement Defects:

Early complement deficiency: Sinopulmonary infection, autoimmune disease.
Late complement component deficiency: Recurrent infection caused by Neisseria species, including meningococcal and gonococcal infection

Most immunodeficiencies present during infancy or early childhood with the most notable exceptions being common variable hypogammaglobulinemia (CVID), selective IgA deficiency, cyclic neutropenia, and complement deficiencies and some of the secondary immunodeficiencies, which may present later in life. Patients with severe combined immunodeficiency (SCID) suffer major infections very early in life, usually during the first weeks or months of age. Congenital agammaglobulinemia typically presents during the second 6 months of life when maternally transferred antibodies wane. Other immunodeficiencies that present clinically before 5 years of age include Wiskott-Aldrich syndrome (WAS), leukocyte adhesion defects (LAD), chronic granulomatous disease (CGD), hyperimmunoglobulin (Ig)M syndrome, ataxia-telangiectasia (AT), and complement deficiencies.

Certain physical findings alert one to the possibility of primary immune deficiency. Failure to thrive secondary to recurrent infections is commonly seen in some antibody deficiencies and combined T and B cell deficiencies. Persistent sinopulmonary infections, especially ear drainage, pneumonia or bronchiectasis, are seen in antibody deficiencies, T and B cell deficiencies and complement deficiencies. Absence or scanty lymphoid tissue such as tonsils and lymph node suggests X-linked agammaglobulinemia (XLA), SCID or complete DiGeorge anomaly. Chronic eczematous rash are found in hyper-IgE syndrome and WAS. Recurrent skin infection with oral ulcers, periodontitis or gingivostomatitis are associated with phagocytic cell defects such as CGD and LAD. Failure or delayed umbilical cord separation is a clinical clue of LAD. Recurrent mucosal candidiasis suggests T cell deficiencies such as SCID and AIDS. Adenopathy and hepatosplenomegaly is frequently encountered in HIV infection.

Several congenital and hereditary conditions with musculoskeletal abnormalities are associated with immunodeficiency. These include Bloom syndrome, Fanconi anemia, trisomy 21, Turner syndrome, short-limbed skeletal dysplasia, cartilage-hair hypoplasia, Shwachman syndrome and ectodermal dysplasia. Classical findings of some specific syndromes should be carefully noted including DiGeorge syndrome (micrognathia, hypertelorism, low-set ears, shortened upper lip philtrum, mandibular hypoplasia, a bifid uvula, an antimongolian slant of the eyes, notched ear pinnae, high arched palate, fish-shaped mouth and congenital heart disease), AT (telangiectasis on bulbar conjunctiva, skin, the bridge of the nose, the ears and antecubital fossa), and Chediak-Higashi syndrome (partial albinism, photophobia).

The proper choice of laboratory tests is based on a careful history and physical examination which target specific suspected immunodeficiency possibilities. A complete blood count is an initial screening test. The number of neutrophils, lymphocytes, abnormalities of white blood cells or red blood cell morphology, numbers and morphology of platelets should be noted. Abnormal CBC findings may point out to a specific disease such as: 1) Lymphopenia (less than 2,000) in XLA, SCID, WAS, AT, DiGeorge, malnutrition and AIDS. 2) Neutropenia in hyper IgM syndrome, cyclic neutropenia, drug-induced neutropenia, Shwachman syndrome and autoimmune-mediated neutropenia. 3) Eosinophilia in WAS, and hyper-IgE syndrome. 4) PMN cells with large cytoplasmic granules in Chediak-Higashi syndrome. 5) Thrombocytopenia in WAS. 6) Howell-Jolly bodies in asplenia. 7) Leukocytosis with few neutrophils in the inflammatory lesions of LAD.

Certain culture results may point out a specific immune defect such as: 1) Encapsulated bacteria in antibody, T cell and complement deficiencies. 2) Opportunistic organisms in T cell deficiencies. 3) Recurrent staphylococcus infections in CGD, LAD and Hyper IgE syndrome. 4) Recurrent catalase-positive organism infections in CGD.

In blood chemistry, a decreased globulin fraction suggests hypogammaglobulinemia, malnutrition, or protein loss. An elevated globulin level is seen in HIV infection, certain autoimmune diseases, hepatitis, myeloma or chronic infections.

If the defect of B cells or humoral immunity defect is suspected, measurements of isohemagglutinins, immunoglobulin levels of IgG, IgA, IgM, specific antibody levels against of diphtheria, tetanus, H. influenzae and pneumococcus, and B cell enumeration (CD19) by a flow cytometer are needed. It should be noted that normal levels of IgG, IgM and IgA in children are lower than that in adults. A second test for specific antibody levels is required after having a booster dose of the vaccine if the first test result is low. Measurement of IgG subclass levels should not be used as a screening test and may not yield any more useful information than a total serum IgG level with

specific antibody titers. In a suspected immunodeficiency case with eczema, IgM and IgE measurement are appropriate to evaluate hyper-IgE syndrome, WAS and atopic dermatitis.

Cellular immunodeficiencies or T cell disorders can be screened in vivo with the use of the delayed hypersensitivity skin test (DHST) including Candida albicans (1:100), tetanus toxoid (1:100), trichophyton (1:30), tuberculin (5TU and 250TU) and mumps (i.e., the anergy panel). An induration of 10mm or more to one antigen or more than one antigen of indurations of 5mm or more indicates normal cell-mediated immunity. Approximately 90% of normal adults show a good response to at least one antigen when three to five antigens are applied. However, DHST may be difficult to evaluate in infants because such immunity has not yet been acquired or because of insufficient sensitization. Other tests for T cell disorders are T cell enumeration including CD3 (pan T), CD4 (helper T cell), CD8 (cytotoxic T cell) by a flow cytometer and in vitro assays for T cell functions such as lymphocyte proliferation to mitogens (phytohemagglutinin, concanavalin-A) and antigens (candida, tetanus, mumps, PPD, streptokinase or toxic shock syndrome toxin). Normally T cells constitute 55% to 80% of peripheral blood lymphocytes, with an absolute count of at least 1,000cells per cu-mm, and the number of CD4 cells is 1.5 to 2 times the CD8 cells. Higher absolute numbers of T-cell subsets and CD4 cells are commonly seen in normal infants and children.

Two screening tests for complement deficiencies are total hemolytic assay, CH50 for the classical pathway and AH50 for the alternative pathway. In a disseminated meningococcemia case or when terminal complement deficiency is suspected, AP50 and properdin levels are indicated if CH50 is normal. If CH50 is completely or partially absent, measurement of C3 and C4 levels is recommended. Normal C3 and C4 levels with low CH50 indicate deficiency of one of the other classic pathway components. If low levels of C3 and C4 are found, increased complement consumption is likely.

Determining the number and morphology of circulatory neutrophils, and assessing the oxidative metabolism by the nitroblue tetrazolium (NBT) test or chemiluminescence test, can screen phagocytic function in clinical practice. If a chemotaxis defect is suspected, a Boyden chamber test is recommended. Adhesion molecules such as CD11 a,b,c/ CD18 on granulocytes should be evaluated if LAD suspected.

Questions

1. The least likely recurrent infection caused by primary immune deficiency is:
    a. Recurrent otitis media
    b. Recurrent bacterial skin infection
    c. Recurrent bacterial pneumonia
    d. Recurrent osteomyelitis
    e. Recurrent urinary tract infection

2. Which one is considered as a characteristic of transient hypogammaglobulinemia of infancy (THI)?
    a. Normal IgG
    b. Normal IgM
    c. Normal IgA
    d. Normal IgD

3. Which one is the most likely diagnosis of an 18 year old female who presents with a history of recurrent sinopulmonary infection, low IgG and IgA and ITP?
    a. X-linked agammaglobulinemia
    b. Severe combined immunodeficiency
    c. Common variable immunodeficiency
    d. Ataxia-telangiectasia
    e. Cystic fibrosis

4. A 7 month old infant with a history of failure to thrive, recurrent oral candidiasis, and Pneumocystis carinii pneumonia is being evaluated. Which of the following is the least useful diagnostic test?
    a. Immunoglobulin levels and functional antibody
    b. Enumeration of T cells and lymphocyte proliferation assay
    c. Anti-HIV antibody
    d. Delayed type hypersensitivity skin test
    e. Nitroblue tetrazolium test and phagocytic tests

5. A mother brings her son, a 6 year old boy with severe eczema, recurrent bacteria skin infections and history of staphylococcal pneumonia for evaluation of immunodeficiency. Initial tests reveal normal CBC and platelets, 50,000 IU of IgE, normal IgG, IgM and IgA levels. Which one is the most likely diagnosis?
    a. Atopic dermatitis
    b. Wiskott-Aldrich Syndrome
    c. Hyper-IgE syndrome
    d. Chronic granulomatous disease
    e. Leukocyte adhesion defect

6. Which one is a true association of a primary immune deficiency and an abnormal hematologic finding?
    a. Leukocyte adhesion defect and thrombocytopenia.
    b. Hyper-IgM syndrome and neutropenia.
    c. Wiskott-Aldrich syndrome and gigantic platelets.
    d. Chronic granulomatous disease and large cytoplasmic granules in PMNs.
    e. Hyper-IgE syndrome and mastocytosis.

7. Which one is the characteristic infection in patients with terminal complement (C5-C9) deficiency?
    a. MRSA
    b. Pneumocystis carinii
    c. Meningococcus
    d. Catalase-positive organisms
    e. Herpes viruses

8. A contraindicated vaccine in an isolated IgA deficiency patient is:
    a. OPV
    b. Varicella
    c. Influenza
    d. MMR
    e. None of the above

9. IVIG replacement is indicated in all of the following, except:
    a. X-linked agammaglobulinemia (XLA)
    b. X-linked hyper-IgM syndrome
    c. Chronic granulomatous disease (CGD)
    d. Wiskott-Aldrich syndrome (WAS)
    e. Common variable immunodeficiency

10. PCP prophylaxis with trimethoprim-sulfamethoxazole is recommended in:
    a. X-linked agammaglobulinemia (XLA)
    b. X-linked hyper-IgM syndrome
    c. Chronic granulomatous disease (CGD)
    d. Wiskott-Aldrich syndrome (WAS)
    e. Hyper-IgE syndrome

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Answers to questions

1.e, 2.c, 3.c, 4.e, 5.c, 6.b, 7.c, 8.e, 9.c, 10.b

Chapter V.6. Hematopoietic Stem Cell Transplantation and Graft Versus Host Disease
Jocelyn M. Sonson

This is a 7 year old female who presents to the office with a chief complaint of a rash on her head, arms and legs. She has a history of acute lymphoblastic leukemia. She had undergone chemotherapy, went into remission and subsequently received an allogeneic stem cell transplantation from her older brother 20 days ago. The rash started 3 days ago on her ears, palms of her hands and the soles of her feet, progressing further to her arms and legs. It has not progressed to involve her trunk or her extremities and there is no desquamation or bullae formation. She denies any GI discomfort, crampy abdominal pain or diarrhea.

Exam: VS T 38, P 100, R 20, BP 118/65. She is alert and active, in no apparent distress. HEENT negative except for the rash. The rash is an erythematous, maculopapular rash on her palms and soles bilaterally, and on the anterior aspects her arms and legs. The rash is also on the nape of her neck. Neck is supple. Chest is clear. Heart regular without murmurs. Abdomen is soft and non-tender. There might be some slight hepatosplenomegaly, but it is difficult to be certain.

She is diagnosed with early graft versus host disease. She is hospitalized and treated with cyclosporine and methylprednisolone for 10 days until the graft versus host disease (GVHD) is controlled. This was followed by a taper of her corticosteroids.

Hematopoietic stem cell transplantation, commonly called bone marrow transplantation (BMT), is indicated for various hematopoietic disorders (aplastic anemia, hemoglobinopathies), storage diseases, and severe immunodeficiencies. Pediatric malignancies that are candidates for stem cell transplantation include acute myelogenous leukemia, acute lymphoblastic leukemia (ALL), chronic myelomonocytic leukemia (CML), lymphomas, neuroblastomas, brain tumors and other solid tumors. Transplantation is recommended only in high-risk situations or when conventional treatment fails. In malignancies such as CML and juvenile myelomonocytic leukemia, hematopoietic stem cell transplantation is used as primary therapy because no other curative treatment exists.

Major sources of stem cells for transplantation include bone marrow, peripheral blood and cord blood. Since the mid-1990s, peripheral blood-derived stem cells have been used with increasing frequency over the traditional marrow cells. Peripheral blood stem cells (PBSC) contain higher numbers of progenitor cells, natural killer cells, and T cells as compared to bone marrow. Studies comparing bone marrow to PBSC transplantation have shown that PBSCs are associated with a shorter period of neutropenia and red blood cell and platelet transfusion dependence, with an equal probability of acute and chronic GVHD. Umbilical cord blood is a new and promising source of hematopoietic progenitor cells with remarkable proliferative potential, which may overcome the limitation of their relatively low absolute cell numbers. Because only a small number of cells are collected, successful transplants are typically limited to smaller sized recipients.

When the stem cells are from an identical twin, the transplant is termed syngeneic. When the stem cells are harvested from the recipient, the transplant is termed autologous. And lastly, when the stem cells are from someone other than the recipient, it is termed allogeneic. The best donors for allogeneic transplantation are siblings who inherit identical human leukocyte antigen (HLA) haplotypes.

Located in the major histocompatibility complex (MHC) on the short arm of chromosome 6, the HLA genes define histocompatibility and determine tolerance of the graft. Although there are over 35 HLA class I and II genes and over 684 alleles, HLA-A, HLA-B (class I), and HLA-DRB1 (class II) genes are used primarily in determining the histocompatibility of donors and recipients for stem cell transplantation. A 6-of-6 match refers to matching these three genes, each of which have two alleles. When none of the 6 alleles match, it is termed a mismatch and the various degrees of mismatch are termed one-antigen mismatch, two-antigen mismatch, etc. When only 3 of 6 alleles mismatch, the term is haploidentical. Graft rejection and graft-versus-host disease (GVHD) are the major immune-mediated complications associated with HLA disparity. The greater the HLA disparity, the higher these risks. Only 25-50% of patients have an HLA-identical sibling, therefore large donor registries have recently been successful in identifying phenotypically matched unrelated donors. In the United States, the National Marrow Donor Program has typed nearly 4 million volunteer donors and uses 118 donor centers and over 57 transplant centers to add 40,000 potential new donors each month.

The initial phase of stem cell transplantation entails the administration of the preparative regimen: chemotherapy and/or radiation therapy. The most common conditioning regimens include total body irradiation (TBI) and cyclophosphamide or busulfan and cyclophosphamide. Other combinations are also used during this conditioning period and include drugs such as etoposide, melphan, carmustine, cytosine arabinoside, thiotepa, ifosfamide, and carboplatin. The combinations are designed to eliminate malignancy, prevent rejection of new stem cells, and to create space for the new cells.

The stem cells infusion takes over an hour, although this time frame depends on the volume infused. Before infusion, the patient is premedicated with acetaminophen and diphenhydramine to reduce the risk of hypersensitivity reaction. The cells are then infused through a central venous catheter. Anaphylaxis, volume overload, and a transient GVHD are the major complications involved.

After stem cell infusion, the primary focus of care is managing the high-intensity preparative regimen. During this period, patients have little or no marrow function and are neutropenic, thus they must depend on transfusions for maintaining erythrocytes and platelets at acceptable levels. Patients are susceptible to life-threatening infections such as herpes simplex virus (HSV) or hospital-acquired nosocomial infections as well as other complications such as veno-occlusive disease, fluid retention, pulmonary edema, and acral erythroderma.

The rate of engraftment is a function of the preparative regimen, the nature and dose of stem cells, and the administration of medications that can suppress recovery. Engraftment, typically defined as a neutrophil count greater than 500 per cubic mm and a platelet count of 20,000 per cubic mm can occur as soon as 10 days to as long as several weeks after infusion. It is during this period that GVHD may occur.

Graft failure and graft rejection of transplanted stem cells, as well as transplanted organs, are influenced by several factors such as HLA disparity, the conditioning regimen, the transplanted cell dose, post-transplant/immunosuppression, donor T cells, drug toxicity and viral infection. Graft rejection may occur immediately, without an increase in cell counts, or may follow a brief period of engraftment. Rejection is usually mediated by residual host T cells, cytotoxic antibodies, or lymphokines and is manifested by a fall in donor cell counts with a persistence of host lymphocytes. Using stem cells from HLA-disparate donors significantly increases the risk for graft rejection/failure.

Transplants for nonmalignant disease generally have more favorable outcomes, with survival rates of 70-90% if the donor is a matched sibling and 36-65% if the donor is unrelated. Transplants for acute leukemias, ALL and AML, in remission at the time of transplant have survival rates of 55-68% if the donor is related and 26-50% if the donor is unrelated . Outcome statistics of autologous transplant for solid tumors are not as good for pediatric malignancies, except for lymphomas.

Graft-versus-host disease (GVHD) is a clinical syndrome that affects recipients of allogeneic stem cell transplants and results in donor T-cell activation against host MHC antigens. There are three requirements for this reaction to occur: 1) the graft must contain immunocompetent cells, 2) the host must be immunocompromised and unable to reject or mount a response to the graft, and 3) there must be histocompatibility differences between the graft and the host.

GVHD can be classified as acute, occurring within the first 100 days after stem cell transplant, or chronic, occurring after the first 100 days. The acute form of GVHD (aGVHD) is characterized by erythroderma, cholestatic hepatitis, and enteritis. aGVHD typically presents about day 19 (median), when patients begin to engraft. It usually starts as either erythroderma or a maculopapular rash that involves the hands and feet and may progress from the top of the scalp down toward the torso, potentially leading to exfoliation or bulla formation. Hepatic manifestations include cholestatic jaundice with elevated values on liver function testing. Intestinal symptoms include crampy abdominal pain and watery diarrhea, often with blood. aGVHD is graded in 5 steps from 0-IV based on involvement of the skin, liver, and GI tract. Grade 0 indicates no clinical evidence of disease. Grade I-IV are graded functionally. Grade I indicates rash on less than 50% of skin and no gut or liver involvement. Grade II indicates rash covering more than 50% of skin, bilirubin 2-3 ml/dL, diarrhea 10-15 ml/kg/d, or persistent nausea. Grade III or IV indicates generalized erythroderma with bulla formation, bilirubin greater than 3 mg/dl, or diarrhea more than 16 mL/kg/d. Survival rates vary from 90% in stage I, 60% in stage II or III, to almost 0% in stage IV.

The development of chronic GVHD (cGVHD), usually occurs after day 100 and resembles a multi-system autoimmune process manifesting as Sjogren's (sicca) syndrome, systemic lupus erythematosus, and scleroderma, lichen planus, and biliary cirrhosis. Recurrent infections from encapsulated bacterial, fungal, and viral organisms are common. The survival rate after onset of chronic GVHD is approximately 42%.

Management of GVHD and graft rejection focuses on both prevention and control of progressive disease. Finding the best HLA matched donor results in the lowest risk of severe disease and rejection. Younger age in either the donor or the recipient is associated with reduced risk. Same gender transplantation is also associated with reduced risk for GVHD. Prophylactic immunosuppression aims to inhibit the host T-lymphocyte activation that mediates rejection and inhibits the donor T-lymphocyte activation that mediates GVHD without altering immunity against infection or malignancy. Because donor T cells are responsible for GVHD, a form of prevention involves depletion of T cells in donor marrows or grafts using monoclonal antibodies or a physical separation technique. Elimination of T cells from the donor graft is an effective approach in some clinical settings, however depletion of T cells allows the persistence of host lymphocytes, which are capable of mediating graft rejection. In addition, loss of donor T cells decreases the benefit of producing a graft-versus-leukemia (GVL) effect and a lower relapse rate.

Treatment of aGVHD focuses on eliminating activated alloreactive T-cell clones. High-dose corticosteroids remain the most effective. Other studied approaches include anti-thymocyte antibodies, anti-TNF and IL-2 receptor antibodies, and immunosuppressive therapy such as cyclosporine, FK506, or mycophenolate mofetil. Treatment for cGVHD should begin with the earliest development of symptoms and requires continued therapy for a minimum of 6 to 9 months, even if symptoms resolve. Therapy for cGVHD includes corticosteroids usually in combination with another agent, often cyclosporine.

Late effects of transplantation can be classified into three basic categories: 1) toxicity from the preparative regimen, 2) toxicity from GVHD, and 3) toxicity from long-term immunosuppression. Clinical conditions include effects on growth and development, neuroendocrine dysfunction, fertility, second tumors, chronic GVHD, cataracts, leukoencephalopathy, and immune dysfunction. The effect of radiation on growth is relatively common and can be a result of a multitude of factors. Disruption of growth hormone production is the most common effect, however thyroid dysfunction, gonadal dysfunction, and bone growth effects also occur due to radiation. Other toxicities include cataracts, azoospermia, and gonadal failure.

Long-term cGVHD effects on the body include disruption of normal glandular function resulting in drying of the eyes, which can lead to corneal injury, and decreased salivary gland production, which can cause severe dental caries. Chronic inflammation of the intestine can lead to strictures and webs. The skin manifestations such as maculopapular rash or a sclerodermatous condition, can extend to all parts of the body and cause fibrosis of the underlying subcutaneous tissues and fascia resulting in contractures.

Continued use of chronic immunosuppressive drugs can cause toxicity that hamper quality of life. These toxicities include hypertension, glucose intolerance, weight gain, growth failure, avascular necrosis of the femoral head, and chronic osteopenia that leads to recurrent fractures. Long-term use of immunosuppressive drugs can lead to recurrent infections, such as bacterial, fungal, cytomegalovirus, adenovirus and varicella zoster.

Questions

1. Which of the following is a requirement for a graft-versus-host disease reaction to occur.
    a. The graft must contain immunocompetent cells.
    b. The host's T-lymphocytes must be able to mount an immune response against the graft.
    c. The host must be immunocompromised
    d. a and b
    e. a and c

2. True/False: The best predictors for developing GVHD are the age and sex of both the donor and recipient.

3. During the conditioning period prior to stem cell transplantation, which of the following purposes does chemotherapy and/or radiation try to accomplish?
    a. Prevent rejection of new stem cells
    b. Create space for new cells
    c. Eliminate malignancy
    d. All of the above
    e. None of the above

4. True/False: A limitation of cord blood as a source for stem cells is the small number of cells collected.

5. During which period does graft-versus-host disease typically occur?
    a. Conditioning
    b. Engraftment
    c. Postengraftment
    d. All of the above
    e. None of the above

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Answers to questions

1. e
2. False. HLA matching is the best predictor.
3. d
4. True
5. b

Chapter VI.1. Virology
Loren G. Yamamoto, MD, MPH, MBA

A 5 year old boy is seen in the office with a history of fever, body aches and nausea. His temperature at home was 39 degrees (102.2 degrees F). He was treated with acetaminophen which resulted in normalization of his temperature and improvement in his body aches. He has been taking fluids without vomiting. He has a slight cough and nasal congestion, but no sore throat, headache, diarrhea, abdominal pain, or urinary complaints.

Exam: T37.2, P80, R25, BP 90/60, oxygen saturation 100% in room air. Height and weight are at the 50th percentile. He is alert, active and cooperative. He is not toxic and not irritable. His exam findings are unremarkable except for nasal congestion.

You tell his mother that he has a virus infection, which is something like a flu type of illness. She says, "That's what he had two weeks ago. How can he keep getting the same virus over and over again? What's the name of this virus anyway? How can he get rid of it?" You explain that this is not the same virus, that there are many different viruses, and that his immune system eventually clears the virus from his system. But he is still susceptible to many other viruses. You're not really sure of the name for his current virus, but we don't have any antiviral treatments for this virus anyway.

While most clinicians have a fairly good background of bacteriology, our knowledge of viruses is usually not as good. Optimal use of antibiotics improves with knowledge of bacteriology. Since we don't have many antiviral agents, it is generally unnecessary (from a therapeutic decision standpoint) to be able to distinguish most of these viruses. However, in the future, as more antiviral agents become available, we will need to improve our knowledge of virology to optimally utilize these future antiviral agents.

Similar to bacteria which can be basically classified using gram stain and morphology, viruses can be classified based on their envelope and nucleic acid type. Viruses are obligate intracellular organisms which utilize the host cell for varying degrees of viral replication. They can only be grown in cell culture media. They are too small to see with a light microscope, but the "cytopathic effect" on the cells in the cell culture media can be seen with a light microscope. Other clinical laboratory methods to identify the presence of viruses are: immunologic assays, antibody serology, polymerase chain reaction (PCR) to detect nucleic acid, detection of reverse transcriptase and electron microscopy.

Viruses are either naked or enveloped. All naked virus have an icosahedral head shape. All enveloped viruses utilize the host cell's membrane by budding off a section to create its envelope. In general, there are four types of disease patterns produced by viruses: 1) acute infection, 2) chronic infection, 3) latent infection, and 4) post-infectious or para-infectious phenomena. Acute infection is caused by naked viruses or enveloped viruses. They kill cells as more viral particles are released. Chronic infection, which is the chronic continued release of viral particles lasting 6 months or more, can only be caused by enveloped viruses such as hepatitis B and HIV. Naked viruses cannot cause chronic infection. Latent infections result when the viral nucleic acid sequence is incorporated into the cell, but the cell is not actively producing viral particles unless it is somehow reactivated in the future. Latent infections, such as with Herpes simplex, are characterized by recurrent episodes of clinical infection. Post and para-infectious phenomena are the result of the body's immune system damaging the host cells and tissues in an effort to get rid of the virus. This is most clinically evident in encephalitis and myocarditis.

The nucleic acid of viruses can be either DNA, +RNA, -RNA, retroviral RNA, or double stranded RNA. DNA viruses usually utilize double stranded DNA (dsDNA) which separates and replicates to form new dsDNA for the new viral particles. Some viruses utilize single stranded DNA (ssDNA). +RNA contains a single stranded RNA which is directly utilized as a messenger RNA (mRNA) to synthesize viral proteins using the host ribosomes. -RNA contains a single stranded RNA which is used as a template for a virion associated polymerase to transcribe an mRNA strand which then uses the host ribosomes to synthesize viral proteins. Retroviral RNA viruses contain a single strand of RNA and a virion associated reverse transcriptase which is used to synthesize dsDNA from the RNA strand. This dsDNA is often integrated into the host cell genome. There are a few exceptions to these general classes.

DNA viruses include parvovirus, papovavirus, adenovirus, hepadnavirus, herpesvirus and poxvirus. This can be remembered by "Poor pappy adds hep to her pox". The first three are naked DNA viruses. The latter three are enveloped DNA viruses.

Parvoviruses commonly cause veterinary disease. The major human parvovirus is called human parvovirus B19. This virus causes Fifth disease (erythema infectiosum), which is a viral exanthem of childhood. Clinical manifestations of Fifth disease are pink cheeks (slapped cheeks), fever and a slight rash on the body. Human parvovirus is a more serious problem for children and adults with hemoglobinopathies (thalassemia, sickle cell disease, etc.). Human parvovirus infection is responsible for aplastic crisis in sickle cell disease. Human parvovirus seems to cause mild anemia in healthy persons, but it causes severe erythrocyte suppression in patients with hemoglobinopathies. A fetus with thalassemia may be stillborn due to hydrops fetalis if the mother is infected by human parvovirus during pregnancy.

Papovaviruses include human papillomavirus and polyomavirus. Papillomaviruses cause various types of cervical cancer and warts such as: plantar warts and genital warts (condyloma acuminata). Polyomaviruses mostly affect birds, but they also include JC virus (which causes progressive multifocal leukoencephalopathy dementia in immunocompromised patients), and BK virus (which causes kidney disease in immunocompromised patients).

Adenoviruses commonly affect children. These illnesses are usually self limited. Many different adenoviruses classified by serotype numbers, cause various combinations of fever, conjunctivitis, pharyngitis, rhinitis, pharyngitis and pneumonia. Some adenoviruses cause gastroenteritis.

The most important hepadnavirus is hepatitis B virus. Since it is an enveloped virus, it is capable of chronic disease in some hosts. Chronic hepatitis B may cause chronic hepatitis, hepatic failure and hepatocellular carcinoma.

Herpesviruses are a large family which include herpes simplex virus (HSV), varicella-zoster virus (VZV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV). HSV and VZV are similar in that they both start with acute infection with subsequent latent lifelong infection and periodic reactivation of symptomatic infection. HSV-1 causes oral herpes while HSV-2 causes genital herpes. Both cause initial acute infections with fever, viremia, mucosal lesions and/or central nervous system infection. The virus survives (latent) in nerve tissue and upon lifelong periodic reactivation, mucosal or vesicular lesions recur. Similarly varicella virus causes an acute systemic infection as varicella (chickenpox), with subsequent reactivation of latent infection manifested as zoster (or shingles). HSV-1 usually causes an initial acute infection characterized by gingivostomatitis (high fever, gum swelling and multiple mouth sores on the lips and anterior tongue). However, some children may present with encephalitis. Neonates are especially prone to encephalitis with HSV-1 and

HSV-2. Thus, all measures must be taken to prevent HSV exposure to neonates. Mothers with a history of genital herpes must undergo Cesarean section prior to the rupture of membranes to prevent neonatal exposure to occult genital herpes lesions.

EBV and CMV are similar in that they both cause syndromes of prolonged viral infection with fever, malaise, lymphadenopathy, and organomegaly. This EBV syndrome is known as infectious mononucleosis, which also includes tonsillitis. EBV is capable of latent infection and is associated with Burkitt's lymphoma (the cells of which contain EBV DNA).

CMV and HSV cause recognizable congenital viral syndromes, which occur when a pregnant mother acquires an initial acute infection with CMV or HSV during early pregnancy. The acute infection results in viremia which may infect the fetus and placenta. This results in a recognizable pattern of findings which include central nervous system calcification, microcephaly, thrombocytopenia, petechial rash, small for gestational age, etc. Recurrent maternal infection does not usually result in a systemic viremia, so congenital infection is not likely with anything other than an acute maternal infection. Congenital infection should be distinguished from perinatal infection in that congenital infection occurs during early gestation while perinatal infection occurs at the time of birth or just after. Thus, a mother with a history of genital herpes many years ago is at no risk for delivering an infant with congenital herpes, but this does pose a risk for perinatal herpes, which may present as an acute encephalitis or overwhelming acute viremia.

The poxviruses do not include VZV (chickenpox) which is in the herpesvirus family. The poxviruses include variola virus (smallpox), vaccinia (cowpox) and molluscum contagiosum virus. Smallpox no longer exists on the planet except in bio-warfare programs. This is a contagious virus with a fairly high mortality rate. Vaccinia virus is called cowpox because it was found in dairy cattle and milk maids would get a mild infection with vaccinia, manifested as pox lesions on their milking hands. Vaccinia virus infection elicits cross immunity against smallpox. The classic observation that milk maids never got smallpox was noticed by Edward Jenner who eventually demonstrated that inoculation with vaccinia virus, could prevent smallpox (variola virus infection), a process which he called vaccination (named after vaccinia virus).

The +RNA viruses (remembered by: "Pete can float toward the coast backward") include picornavirus, calicivirus, flavivirus, togavirus, coronavirus, and retroviruses (retro = backward in the mnemonic).

Picornaviruses include (PEECoRnA) polio, entero, echo, coxsackie, rhino and hepA virus genera. Polio is covered in a separate chapter. Enteroviruses cause viral meningitis, occasional encephalitis, gastroenteritis and myocarditis. Coxsackie virus usually causes fever and stomatitis, such as in hand-foot-mouth disease. Echovirus causes fever and rash. Rhinoviruses cause common cold symptoms.

Caliciviruses include Norwalk virus (which causes gastroenteritis) and hepatitis E virus. Flaviviruses include hepatitis C, yellow fever, dengue fever and St. Louis encephalitis. Togaviruses include the equine encephalitis viruses (such as western equine encephalitis and eastern equine encephalitis), and rubella virus (German measles). Coronaviruses include multiple serotypes which cause cold symptoms.

Retroviruses include human immunodeficiency virus (HIV) and human T-cell lymphotrophic virus.

The -RNA viruses (remembered by: "raspberry filled parfaits are often burned") include rhabdovirus, filovirus, paramyxovirus, arenavirus, orthomyxovirus and bunyavirus families. Rabies is the most important rhabdovirus. Ebola virus is the most important filovirus. Paramyxoviruses include rubeola (measles), mumps, respiratory syncytial virus (RSV), and parainfluenza virus (colds, laryngitis, croup). Arenaviruses include lymphocytic choriomeningitis virus and Lassa fever virus. Orthomyxoviruses include influenza A and B. Hanta virus is the most important bunyavirus.

The -RNA viruses include several deadly viral infections: rabies, Ebola and Hanta viruses. This group also includes many illnesses for which we are routinely immunized against: measles, mumps, and influenza. Premature and other high risk infants routinely receive passive immunity against RSV.

The double stranded RNA viruses include orbivirus, rotavirus and reovirus (ORR). Orbivirus includes Colorado tick fever. Rotavirus is a major cause of pediatric diarrhea. Reoviruses causes febrile illnesses without other specific findings.

Summary of virus classifications

I. DNA viruses (Poor pappy adds hep to her pox)
   - A. Naked
     1. Parvovirus (human parvovirus B19)
     2. Papovavirus (papillomavirus, polyomavirus)
     3. Adenovirus (many which cause febrile respiratory infections)
   - B. Enveloped
     1. Hepadnavirus (hepatitis B)
     2. Herpesvirus (HSV, VZV, EBV, CMV)
     3. Poxvirus (variola, vaccinia, molluscum contagiosum)

II. +RNA viruses (Pete can float toward the coast backward)
   - A. Naked
     1. Picornavirus (PEECoRnA = polio, entero, echo, coxsackie, rhino, hepA)
     2. Calicivirus (Norwalk, hepatitis E)
   - B. Enveloped
     1. Flavivirus (yellow fever, dengue, St. Louis encephalitis, hepatitis C)
     2. Togavirus (rubella, equine encephalitis)
     3. Coronavirus (colds)
     4. Retrovirus (HIV)

III. -RNA viruses (raspberry filled parfaits are often burned)
- A. Naked - none
- B. Enveloped
  1. Rhabdovirus (rabies)
  2. Filovirus (Ebola)
  3. Paramyxovirus (measles, mumps, RSV, parainfluenza)
  4. Arenavirus
  5. Orthomyxovirus (influenza)
  6. Bunyavirus (Hanta)

IV. dsRNA viruses (ORR)
- A. Orbivirus (Colorado tick fever)
- B. Rotavirus
- C. Reovirus

Questions
1. Name the 3 naked and 3 enveloped DNA virus families.
2. In terms of the potential duration of infection, how do naked viruses differ from enveloped viruses?
3. Name 6 viruses within the picornavirus family.
4. How are members of the herpesvirus family similar?
5. Name 4 viruses which cause cold symptoms?
6. Name the +RNA viral families.
7. Name two naked (non-enveloped) viruses which cause chronic infection.
8. Name the -RNA viral families.
9. Naked viruses are mostly of what morphologic shape on light microscopy?
10. Name 4 virus families which cause central nervous system infections.

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Answers to questions
1. Poor pappy adds hep to her pox: Parvovirus, papovavirus, adenovirus, hepadnavirus, herpesvirus, poxvirus. The first three are naked, the latter three are enveloped.
2. Naked viruses cause acute infection only. Some enveloped viruses are capable of chronic infection.
3. PEECoRnA: polio, entero, echo, coxsackie, rhino, hepA.
4. VZV and HSV are similar in that they both cause acute vesicular infections with lifelong latency and recurrence. EBV and CMV are similar in that they both cause infectious mononucleosis type syndromes. CMV and HSV both cause congenital viral infection malformation syndromes.
5. Rhinovirus, RSV, parainfluenza virus, coronavirus, adenovirus. Influenza virus may be included also.
6. Pete can float toward the coast backward: picorna, calci, flavi, toga, corona, retro.
7. None. Only enveloped viruses can cause chronic infection.
8. Raspberry filled parfaits are often burned: rhabdo, filo, paramyxo, arena, orthomyxo, bunya.
9. Viruses are too small to be seen on light microscopy. On electron microscopy, nearly all naked viruses have an icosahedral shape.
10. Herpesvirus (HSV, VZV, CMV), picornavirus (poliovirus, enteroviruses), flavivirus (encephalitis), togavirus (encephalitis), rhabdovirus (rabies), bunyavirus (encephalitis).

Chapter VI.2. Basic Bacteriology
Loren G. Yamamoto, MD, MPH, MBA

You arrive at your clinic in the morning and a nurse tells you that the lab has called with three positive culture reports. The nurse hands you the lab reports and the patients' charts.

The first culture is a beta strep, not group A. This is a throat culture from a 10 year old boy seen in the clinic yesterday for a sore throat. He was treated with penicillin pending the outcome of the culture. You know that group A strep should be treated for 10 days, but you ask your associate what to do about non-group A beta hemolytic strep. He tells you that non-group A strep in the throat is non-pathogenic.

The second culture is a blood culture with gram positive rods. This is from a 14 month old male who was seen in the clinic 3 days ago with fever. A CBC was normal at the time. He was treated with fever medications and no antibiotics. You call his home and his mother says that he has not had any fever for the past two days. He is now well and he seems back to his usual self. He comes to the clinic for a follow-up exam and you determine that he is no longer ill. You conclude that this organism must be a non-pathogen (i.e., a contaminant of the blood culture bottle).

The third culture is a urine culture with 100,000 colony forming units (cfu) per ml of gram negative rods. This is an 18 month old female who presented with fever and vomiting. Her UA showed 25-50 wbc's per high powered field (hpf). She was treated with IM ceftriaxone and oral cephalexin. She is seen in follow-up later today and she is doing well. Her antibiotics are continued. Her urine culture the next day identifies the organism as E.coli which is sensitive to cephalosporins.

Basic microbiology knowledge can be very useful clinically if one focuses on the clinically important aspects of bacteriology. It can greatly help in the preliminary management of patients before definitive identification of the organisms and antibiotic sensitivities are determined.

Gram stain morphology results are the first step in identification. Gram positive cocci and gram positive rods greatly narrow the possibilities. Gram negative organisms are more difficult to narrow down.

Gram positive cocci are either staphylococci or streptococci. One could distinguish these morphologically since staph are usually arranged in clusters, while strep are usually arranged in pairs and/or chains. The catalase assay is more reliable since staph are catalase positive and strep are catalase negative. There are only two types of clinically important staph species, Staph epi and Staph aureus. These two are distinguished by the coagulase test. Staph epi is coag negative, while Staph aureus is coag positive. Aureus means "gold", because most Staph aureus colonies (growing on a Petri plate) have a gold color, while most Staph epi colonies have a white color. Staph aureus is methicillin and cephalosporin resistant about 25% of the time. MRSA (methicillin resistant Staph aureus) are similarly resistant to oxacillin, cloxacillin, nafcillin, dicloxacillin and cephalosporins. Staph epi is methicillin and cephalosporin resistant over 90% of the time. Vancomycin can be used for resistant Staph epi and Staph aureus.

Staph epi is usually not a clinical pathogen and it is frequently a contaminant in blood cultures. If Staph epi grows from a blood culture, it is more likely to be a contaminant if the patient is healthy and doing well by the time the culture comes back. Staph epi growing from a blood culture is more likely to be a true pathogen if the patient has any type of indwelling plastic or prosthetic materials, such as a ventriculoperitoneal shunt, a central venous catheter, etc., since Staph epi has a propensity to adhere to indwelling plastic devices forming slime layers of bacterial colonization onto the device which often requires removal of the device since antibiotic treatment alone is often insufficient to eradicate the colonization.

Staph aureus frequently causes skin and soft tissue infections, such as cellulitis, impetigo and abscesses. Staph aureus is a common cause of more serious infections such as septic arthritis, osteomyelitis, discitis, severe pneumonia, etc. Staph aureus can produce an exotoxin which can result in septic shock but additionally, these toxins can cause several clinical entities depending on the type of toxin produced. Toxic shock syndrome (TSS) is due to a staph aureus toxin which causes an erythroderma (commonly mistaken for scarlet fever), high fever and shock. Staphylococcal scalded skin syndrome (SSSS) toxin causes a generalized exfoliative desquamation and severe infection. Bullous impetigo causes localized blistering due to a less virulent exfoliative toxin. Staph aureus food poisoning is a heat stable toxin that results in vomiting and diarrhea very soon after the ingestion of contaminated food containing pre-formed toxin.

When a blood culture grows Staph aureus, it should always be considered to be a serious pathogen. Empiric coverage with IV vancomycin should be started for potentially serious Staph aureus infections until culture and sensitivities are known, since the resistance rate to methicillin and cephalosporins is too high (at least 25%). However, if the Staph aureus infection is deemed less serious, such as impetigo or a small abscess, treatment with a cephalosporin (75% sensitive) or clindamycin (95% sensitive) may be satisfactory.

Streptococci are first classified using their hemolytic pattern on sheep blood agar. Clear colonies are called beta hemolytic. Green colonies are called alpha hemolytic. Streptococcal colonies which do not result in any hemolysis are called non-hemolytic or gamma hemolytic. For the most part, non-hemolytic strep are not clinically important since they don't cause much clinical disease. Alpha hemolytic strep include Strep pneumoniae (pneumococcus), Strep viridans, and other miscellaneous non-pathogenic alpha strep (often found in mouth and nasal flora). Strep pneumoniae and Strep viridans can be distinguished by several lab sensitivity tests to bile and Optochin.

Pneumococci cause many human infections including pneumonia, meningitis, sinusitis, otitis media, occult bacteremia, primary peritonitis, sepsis, osteomyelitis and septic arthritis. Some pneumococci contain polysaccharide capsules which add virulence to the organism. Non-encapsulated pneumococci are less virulent and are often implicated in otitis media or other minor infections. Severe pneumococcal infections are usually due to encapsulated pneumococci. The immune system forms antibodies against the polysaccharide antigens. Pneumococcal vaccines are developed against these polysaccharide serotypes. Several multivalent pneumococcal vaccines are currently available. Pneumococcus is usually sensitive to penicillin, but resistance is emerging requiring treatment with higher penicillin doses, cephalosporins or for high level resistance, vancomycin is required. Strep viridans (not a species, but rather a group of organism species) is a less common human pathogen, sometimes causing bacterial endocarditis.

Beta hemolytic strep are further classified using the Lancefield classification, which utilizes letters. Group A strep (also known as Strep pyogenes) causes strep pharyngitis, tonsillitis, impetigo, scarlet fever and cellulitis. It occasionally causes pneumonia, endocarditis and necrotizing fasciitis (commonly called the flesh eating bacteria syndrome). Group A strep are still penicillin sensitive. Post-infectious complications include acute rheumatic fever and acute glomerulonephritis.

Group B strep (also known as Strep agalactiae) commonly colonizes the maternal gyn tract. Newborns are exposed to this, so group B strep is a common cause of neonatal pneumonia, meningitis and sepsis. Maternal infections with group B strep include chorioamnionitis

and endometritis. Since this organism is common and potentially highly virulent, mothers are currently screened for group B strep routinely and if found, they are given ampicillin prophylaxis to reduce the risk of neonatal sepsis. Group B strep are still penicillin sensitive. They are sensitive to cephalosporins, but less so, such that treatment with penicillin or ampicillin is still recommended even in neonates treated with cephalosporins.

Terminology such as "beta strep" or "group A strep" may be considered incomplete. Technically, beta strep is not the name of an organism since there are many different types of beta hemolytic strep (group A, B, C, D, etc.). However, "group A strep" is unambiguous, since by definition, only beta hemolytic strep can be group A. Thus, it is not necessary to say "group A beta hemolytic strep", since "group A strep" will suffice. It is only sufficient to say "beta hemolytic strep" or "beta strep" if your intention is to refer to all beta hemolytic strep, but this does NOT refer to a single specific organism.

Group C strep are less pathogenic. They are sometimes found in the pharynx. While group C strep may cause pharyngitis, such infections are almost always self limited without suppurative or post-infectious complications. Thus, antibiotic treatment with penicillin may be used to treat non-group A beta hemolytic strep pharyngitis (such as group C strep) if the patient is symptomatic with a sore throat or fever, but it is not absolutely necessary since such infections are generally self limited.

Group D strep is a confusing group, because this is the only group which does not name a single organism. There are two important group D strep organisms; Strep faecalis and Strep bovis. The term "enterococcus" is often used to refer to Strep faecalis; however "enterococcus" can be Enterococcus faecalis (new name for Strep faecalis), Enterococcus faecium or others. Additionally, group D strep are not always beta hemolytic. Thus, group D strep are identified on a separate plate (other than sheep blood agar) for identification. Group D strep are difficult to treat, often requiring two drug therapy such as ampicillin and an aminoglycoside. You may see the abbreviation "VRE" which stands for vancomycin resistant enterococci.

Gram positive rods are uncommon causes of human infection. Lactobacilli may be found in urine. Diphtheroids are frequent contaminators of blood cultures. Clostridium, corynebacteria, bacillus and listeria are all capable of causing severe disease, but these are all uncommon infections. They are generally penicillin sensitive (with the exception of Clostridium difficile). Clostridium and bacillus species are spore formers. These dormant spores are highly resistant to environmental stress such as dehydration and heat, making it difficult to eradicate the infectious particles from the environment.

Clostridium are anaerobes which produce disease through exotoxin production. C. tetani and C. botulinum produce potent neurotoxins. Children are routinely immunized with tetanus toxoid. Botulism is prevented by strict regulation of canned goods (heat and/or pressure cooking requirements), but infant botulism may still occur from exposure to spores (usually from soil or foods). C. difficile (penicillin resistant) produces a toxin which causes pseudomembranous colitis, which results from gastrointestinal C. difficile overgrowth with prolonged broad spectrum antibiotic treatment. C. perfringens causes cellulitis and tissue gas gangrene (tissue necrosis results from exotoxin production).

Corynebacterium diphtheria causes a severe throat infection, but its exotoxin is cardiotoxic and neurotoxic. Immunization with diphtheria toxoid prevents the toxin effects and severe infection. Listeria monocytogenes is an uncommon infection which may be transmitted in foods (commonly deli meats and cheese). It produces mild gastroenteritis in most individuals, but it may cause sepsis in pregnant women, neonatal sepsis, and severe infections in immunocompromised patients.

Bacillus species, are aerobic gram positive rods. The major pathogen is bacillus anthracis which is an uncommon organism except when used for biological warfare. It can cause cutaneous anthrax (localized necrotic infection) or anthrax pneumonia (high mortality).

Gram negative organism species are more numerous. They generally produce endotoxins, as opposed to the exotoxins produced by many gram positive organisms. Their laboratory identification methods are more complex and beyond the scope of this chapter.

The most common gram negative rods are those found in the GI tract, commonly called the Enterobacteriaceae. Human disease from these organisms most commonly originates from the GI tract. Urinary tract infection (UTI), neonatal sepsis and peritonitis most commonly result from exposure to stool organisms. The most common organism involved is Escherichia coli. E. coli is the most common cause of UTI and a common cause of neonatal sepsis (along with group B strep). Normal flora gram negative rods include E. coli, klebsiella, proteus, serratia, etc. These can sometimes causes disease, but usually because they have entered the wrong part of the body (such as UTI, neonatal sepsis and aspiration pneumonia). Most E. coli are normal flora, but some E. coli subtypes are pathogenic such as E. coli 0157 (causes dysentery and hemolytic uremic syndrome), enterotoxigenic E. coli (causes traveler's diarrhea) and enteropathogenic E. coli (causes pediatric diarrhea). Pathologic gram negative rods include salmonella, shigella, yersinia, pseudomonas, etc. Most gram negative rods are covered by aminoglycosides, cephalosporins, broad spectrum penicillins, sulfonamides and quinolones. Pseudomonas is particularly resistant so it commonly emerges in patients treated with prolonged courses of antibiotics.

Gram negative cocci are basically Neisseria and Moraxella species. Moraxella catarrhalis is part of the upper respiratory tract normal flora. It is commonly found in otitis media and sinusitis. It is usually treated with a broad spectrum penicillin such as amoxicillin, but some M. catarrhalis are resistant.

Neisseria meningitidis (also called meningococcus) is highly virulent causing meningitis and meningococcal sepsis (known as meningococcemia). Meningococcus contains a polysaccharide capsule adding to its virulence. A meningococcal vaccine directed against the polysaccharide capsule is available. Neisseria gonorrhoeae (also called gonococcus or GC) is sexually transmitted causing urethritis, epididymitis cervicitis, pelvic inflammatory disease and pharyngitis. Disseminated GC causes polyarticular and monoarticular septic arthritis. Infants exposed to GC may develop ophthalmia neonatorum. All newborns receive routine eye prophylaxis with ophthalmic silver nitrate or antibiotics. Meningococcus is still penicillin sensitive. GC used to be penicillin sensitive, but most GC today are penicillinase producing (known as penicillinase producing Neisseria gonorrhoeae, or PPNG for short). PPNG can still be treated with ceftriaxone, doxycycline or azithromycin.

Haemophilus species used to be a major pediatric pathogen. They are gram negative organisms commonly called coccobacilli, or pleomorphic (variable forms) rods. Haemophilus influenzae (H.flu) is either capsulated (only one major polysaccharide serotype called type B) or non-encapsulated. Haemophilus influenzae type B (known as HiB for short) was a major cause of sepsis, meningitis, septic arthritis, pneumonia, epiglottitis and cellulitis in young children. These serious and life threatening infections from HiB have largely been eliminated from our community through widespread HiB immunization (a major public health and pediatric accomplishment). This is a polysaccharide vaccine which does not provide immunity against non-encapsulated (also called non-typable H.flu). Since non-typable H.flu does not have a polysaccharide capsule, it is less virulent, so it is associated with only minor infections such as otitis media and sinusitis. H.flu (non-typable and type B) is 30% resistant to amoxicillin, due to beta-lactamase production. Anti-beta-lactamase drugs (clavulanic acid, sulbactam, etc.) overcome this resistance. Thus, amoxicillin-clavulanic acid and high generation cephalosporins cover 100% of H.flu.

Gram negative anaerobes typically cause polymicrobial infection. Most anaerobes are sensitive to penicillin with one major exception and that is Bacteroides fragilis (B.frag), which is commonly found in bowel (stool). Anaerobes cause a putrid (foul decay) odor (e.g., feces). Esophageal and mouth anaerobes typically do not contain B.frag., which is why most texts refer to anaerobe infections above the diaphragm (B.frag unlikely) versus anaerobe infections below the diaphragm (B.frag is likely). Thus, classically, the anaerobe component of aspiration pneumonia may be treated with penicillin as opposed to peritonitis due to a ruptured appendix which is likely to involve B.frag. Bacteroides fragilis is classically treated with clindamycin, metronidazole or chloramphenicol. Some cephalosporins such a cefoxitin and cefotetan have better coverage against B.frag, but they are not 100%. If an anaerobic infection is suspected, culture samples must be sent to the lab in special anaerobic culture/transport media (e.g., thioglycolate).

Other gram negative organisms that deserve mention include Legionella, Bordetella, Brucella, Francisella, Campylobacter, Helicobacter, Vibrio and Pasteurella. Spirochetes include Treponema (syphilis, yaws, etc.), Borrelia (Lyme disease) and Leptospira (leptospirosis).

Mycobacterium species do not stain well with the gram stain. They stain best with the acid-fast stain. Mycobacterium tuberculosis causes tuberculosis. M. leprae causes leprosy (Hansen's disease). M. avium-intracellulare causes pulmonary infections in immunocompromised patients. M. marinum is a marine organisms which causes "fish tank" granulomas in those who are frequently exposed to aquarium and marine environments.

Mycoplasma and Chlamydia are similar to viruses in that they are obligate intracellular organisms. They cannot be grown on Petri plates because they require cells to grow. Mycoplasma and Chlamydia must be grown in cell media (similar to viruses) in labs, thus, they are difficult to culture. Despite their obligate intracellular requirements, they utilize bacterial DNA ribosomes and are thus, susceptible to erythromycins, tetracyclines and some quinolones. The epidemiology of infections with Mycoplasma and Chlamydia is unclear since these organisms are difficult to identify definitively. It was once thought that Mycoplasma pneumonia only occurred in young adults, but it is now known to occur in all age groups, although its frequencies in each age group are unclear. It was once thought that Chlamydia infections were largely limited to an eye infection called trachoma. However, it is now known that Chlamydia causes respiratory infections and pelvic inflammatory disease. The true epidemiology of these organisms is still unclear. They may play a role in many other infections that we have yet to discover. Other obligate intracellular organisms include Rickettsia (Rocky Mountain Spotted Fever, typhus), Coxiella, Ehrlichia, and Bartonella (not intracellular).

Summary Table:

Gram Positive Cocci:
- Catalase (+) Staph:
  - Coagulase (+) Staph aureus
  - Coagulase (-) Staph epidermidis
- Catalase (-) Strep:
  - Alpha hemolysis on sheep blood agar (green colonies):
    - Bacitracin sensitive: Strep pneumoniae (pneumococcus)
    - Bacitracin resistant: Strep viridans
  - Beta hemolysis on sheep blood agar (clear colonies):
    - Group A (Strep pyogenes)
    - Group B (Strep agalactiae)
    - Group C (not very pathogenic)
    - Group D (not always beta hemolytic)
      - Strep faecalis (enterococcus)
      - Strep bovis

Gram positive rods:
- Clostridium (tetanus, botulism, perfringens, difficile)
- Corynebacterium (diphtheria)
- Listeria monocytogenes
- Bacillus (anthracis)
- Lactobacillus
- Diphtheroids (flora)

Gram negative cocci:
- Neisseria (gonorrhoeae, meningitidis)
- Moraxella

Gram negative rods:
- Enteric gram negative rods (E. coli, Proteus, Klebsiella, Serratia, etc.)
- Pathologic gram negative rods (Salmonella, Shigella, Yersinia, Pseudomonas, etc.)

Gram negative coccobacilli:
- Haemophilus influenzae

Gram negative anaerobes:
- Bacteroides fragilis (penicillin resistant)
- Most others (penicillin sensitive)

Spirochetes:
- Treponema, Borrelia, Leptospira

Acid-fast bacilli:
- Mycobacterium (TB, leprae, avium-intracellulare, marinum)

Non-viral obligate intracellular organisms:
- Mycoplasma
- Chlamydia
- Rickettsia
- Other: Coxiella, Ehrlichia, Bartonella (not intracellular)

Questions

1. A lab slip returns which says "coag negative staph". What does this mean and what is the likelihood that this organism is sensitive to methicillin and cephalosporins?
2. At laparotomy, a patient is found to have a ruptured appendix and peritonitis. A swab from the peritoneal fluid is expected to grow what types of organisms? Is there any special swab or sample that must be sent to properly culture this fluid?
3. Name two characteristics of anaerobic infections?
4. Name 5 disease conditions which result largely from toxin production?
5. Group A streptococcal pharyngitis is usually a self limited infection even without antibiotic treatment. What is the reason for treating "strep throat"?
6. A lab tech identifies beta hemolytic colonies on a sheep blood agar plate. What is the next step to identify the organism?
7. Two days after a blood culture is drawn, the lab reports gram positive cocci. This patient is a 10 month old with fever and no other identifiable clinical infection. The child is now afebrile and looks good. What organism possibilities could be growing in this blood culture?
8. A lumbar puncture is done on a very ill 8 month old infant. The fluid is cloudy and the gram stain shows many WBCs and gram positive cocci. What organism is likely causing the meningitis? What organism would be likely if the gram stain showed gram negative cocci instead?
9. A new resident on the pediatric service orders a gram stain on a stool sample. What is the result likely to be?
10. If staph epi grows from a blood culture, how can one determine whether this is a contaminant or a staph epi bacteremia?

References

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Answers to questions

1. This is Staph epi which is almost always resistant to methicillin and cephalosporins.
2. The peritoneal fluid is likely to grow multiple stool organisms. E. coli will predominate. A polymicrobial anaerobic infection is also likely. To properly culture anaerobes, an anaerobic culture swab sent in special anaerobic media (e.g., thioglycolate) must be sent.
3. They are usually polymicrobial and they have a foul odor.
4. Tetanus, botulism, diphtheria, toxic shock, staphylococcal scalded skin syndrome, scarlet fever, etc.
5. Early antibiotic treatment results in a slightly shorter course of symptoms, but the main reason to treat is to prevent suppurative complications and rheumatic fever.
6. Lancefield classification to determine if this organism is group A, group B, etc.
7. Pneumococcus or Staph epi (contaminant).
8. Most likely gram positive cocci is pneumococcal meningitis. Most likely gram negative cocci is meningococcal meningitis.
9. This is an inappropriate order. The stool will be full of enterobacteriacae, anaerobes, and enterococcus. The gram stain will show mostly gram negative rods and perhaps a few gram positive cocci.
10. It is not possible to determine this with certainty in most instances. However, healthy patients who are no longer ill by the time the culture comes back are unlikely to have had Staph epi bacteremia. Thus, in these patients, the Staph epi is most likely a contaminant. In patients with indwelling plastic (central catheters, ventriculoperitoneal shunts), it should be assumed that the Staph epi is a clinically important infection, probably colonizing the plastic tubing.

Chapter VI.3. Fever
Marian E. Melish, MD

A 15 month old boy is brought to the office by his very concerned mother who reports that he has a high fever which doesn't come down even with double doses of acetaminophen and a cold water bath. He has had fever for 24 hours. His temperature has been measured as high as 40.8 degrees (105.4 degrees F). His mother and grandmother have given acetaminophen as directed on the package. When his fever remained over 40 degrees (104 F), they gave a second dose one hour after the first during every 4 hour period over the past day. His last dose was 1 hour prior to your exam. He has also been placed in a cold water bath but he objected so forcefully that it lasted only 5 minutes. Despite the fever he has been playing with his toys but has refused solid foods. He has had some juice. He has urinated slightly less often than usual. He has not vomited, had one normal formed stool today, and does not appear to be in pain although he is more fussy than usual and he appears tired. His mother notes that he is getting a new molar.

His past medical history, family history and review of systems are unremarkable.

Exam: VS T 40.7 (105.3 degrees F), P 185, R 24, BP 95/56, oxygen saturation 99%. He is alert and active, sitting on the exam table playing with a toy car. His movements appear jerky. He cries immediately when touched with a stethoscope and vigorously resists examination. The physical exam is otherwise unremarkable except for the fever and tachycardia.

Your nurse urgently requests permission to give him a dose of ibuprofen and a cold water bath to lower his temperature. His mother is crying, saying, "Do something! The temperature keeps going up. He will go into convulsions or develop brain damage!" What should you do?

Fever is a fascinating phenomenon, highly conserved throughout the animal kingdom as a response to infection and inflammation. Fever in children is associated with many myths and fears which are widely shared by lay people and medical professionals alike. This chapter will review what is known about this "hot topic" and suggests an approach to the questions and concerns above.

Fever is a state of elevated core temperature caused by a complex and highly regulated host response involving cytokines and numerous other acute phase reactants with activation of physiologic, endocrine and immune systems. It is stimulated by the presence of an infectious or inflammatory trigger. The interactions of these triggered host factors result in a change in the normal temperature range which is usually tightly controlled. Fever as a response to an infectious or inflammatory stimulus must be distinguished from hyperthermia caused by exposure to extreme environmental conditions or pathologic responses to anesthetics or drugs.

The measurement of true core temperatures is too invasive for routine clinical use. Core temperatures are best measured in the pulmonary artery or by a deep colonic probe. Even these invasive measurements are not accurate for all parts of the body. For example, in shock or other poor peripheral perfusion states, the temperature of the peripheral sites may be much lower than the core. Conversely, during vigorous exercise the muscle temperature may be considerably higher than the core. There are accuracy problems with all of the proposed formulas for converting a measured temperature at any one site with the temperature at another site or with the theoretical core temperature. Therefore conversion is neither necessary nor appropriate.

The oral temperature as measured under the tongue is the most accurate and practical site for thermometry. Rectal temperature measurements are preferred in infants and children who are too young to cooperate with oral measurements. Rectal temperature measurements are a mean of 0.4 C (0.7 F) degrees higher than oral temperatures. As rectal temperature readings may be affected by the presence or absence of stool in the rectum and peculiarities of local blood flow, oral temperature readings are considered to be the best reflector of core temperature. Tympanic temperature measured with a probe against the tympanic membrane as commonly employed by anesthesiologists is very accurate compared with other core temperature measurements. Recently infrared ear thermometers have become popular because they give very rapid readings. However these commonly available infrared ear thermometers used in clinics, hospital wards, and homes are somewhat inaccurate and show significant variation between measurements. They may read falsely low if the seal in the ear canal is poor (1). I have also encountered falsely elevated readings in multiple patients especially when the instrument is older or malfunctioning. Therefore, an unexpected elevated reading from an infrared ear thermometer should be confirmed with an oral or rectal measurement before embarking on an investigation of fever. Once it is proven that the patient has a fever, infrared ear readings may be used to measure trends in temperature associated with therapy of the basic process as long as one remembers that ear readings are variable and less accurate. Axillary temperature measurements are less accurate. Axillary temperature accuracy can be improved by keeping the thermometer in place for 5 to 12 minutes and holding the arm flexed against the body for the entire period. Skin temperature as measured with temperature sensitive crystals implanted in a strip can approximate the body's temperature, but should not be relied upon to give an accurate temperature.

In two studies, elevated tactile temperatures as measured at home by mothers touching their child's forehead had moderate (46% to 73%) correlation with later documentation of fever in the ED or hospital (2,3). Therefore if tactile fever is reported, later confirmation of either elevated temperature or an abnormal clinical appearance is needed before embarking on an etiologic investigation (4).

The first comprehensive study of temperature variation was published in 1868 by Carl Wunderlich (5,6). It is still the most comprehensive study and involved nearly one million observations in 25,000 subjects. He demonstrated that normal individuals have a range of temperature readings and that there is a diurnal variation with the lowest daily reading falling between 2 and 8 a.m. and the highest readings recorded from 4 to 9 p.m. These studies established the definitions of 37 C (98.6 F) degrees as the normal mean value and 38 C (100.4 F) as the fever threshold. More recent studies using more modern instruments found normal oral temperature to vary between 35.6 C (96.0 F) to 38.2 C (100.8 F) in 700 observations of a sample of 148 normal well young adults. In these adults, the 99th percentile of readings was 37.7 C (99.9 F), the median was 36.8 C (98.2 F), the mode was 36.7 C (98.0 F), and only 8% of the readings were at Wunderlich's normal temperature point of 37 (98.6) (6). These studies confirmed Wunderlich's finding of diurnal variation. Temperature was lowest at 0600 hours and peaked in late afternoon between 1600-1800. The mean difference between lowest and highest daily temperatures in these adult subjects was 0.5 degree C (0.9 degree F). For each individual, there existed a characteristic narrow range or normal set-point of body temperature showing diurnal variation of 0.1 to 1.3 degree C. Body temperature is affected very little by environmental conditions but to a greater degree by vigorous exercise. For a population of normal adults, the range of oral body temperature measurements is wider than the individual variation of 0.5 C, spanning 35.6 to 37.8 C (96.0 to 99.9 F) (the 1st to 99th percentiles) (6). A systematic review of articles published from 1939-1990 showed the range for normal oral temperatures to be somewhat wider 33.2 to 38.2 C, (men: 35.7 to 37.7 C, women: 33.2 to 38.1 C) (7).

There has been less systematic study of normal temperatures in children. It has been suggested that preschool children have a more exaggerated diurnal difference in than adults with higher temperatures late in the afternoon or after physical activity (8). A study of rectal temperatures taken once throughout the day in 671 well infants < 3 months old demonstrated (9):

Age in days	Mean temperature C	Mean + 2 SD
Birth - 30 days	37.4	38.0
31-60 days	37.5	38.1
61-91 days	37.6	38.2

The eruption of new teeth was shown to be associated with a slight increase in temperature within the normal range in 2 studies (10,11). A third study found no evidence for temperature elevation with tooth eruption or the 5 days preceding (12). There is no evidence that teething causes an elevation into the febrile range. The idea that teething causes fever is a widespread folk belief shared by a majority of parents and pediatric dentists but by less than 10% of pediatricians (13).

It remains somewhat uncertain exactly where the febrile range begins but oral temperatures greater than 37.7 degrees C (99.9 F) are greater than the 99th percentile for normal adults. Many lay people and health care professionals regard oral temperature readings between 37 and 38 degrees C (98.6 to 100.4 F) as "low grade fever." This is inappropriate as these values fall within the normal adult range in multiple studies. Temperature readings above the range of 38 to 38.2 C (100.4 -100.8 F) by any route suggest the presence of fever. This definition of the fever threshold is convenient and generally accepted. Certain individuals may have temperature elevations greater than this while being entirely well especially in late afternoon or after vigorous exercise. The presence of sustained fever of any degree indicates a problem which may need evaluation. Recognizing the presence of fever is of significance, but concern about the height of the fever is of less importance since the height of fever by itself is of limited diagnostic value.

Physiology of Fever: Fever producing substances are divided into two categories: those produced outside the body (exogenous pyrogens) and those produced inside the body (endogenous pyrogens). Exogenous pyrogens are usually microorganisms, their components or their extracellular products. Endogenous pyrogens are host cell derived cytokines which are the principal central mediators of the febrile response. The secretion of endogenous pyrogens is induced by both exogenous pyrogens and many endogenous molecules such as antigen-antibody complexes, complement, steroid metabolites, certain bile acids, and many lymphocyte derived molecules. The most prominent currently recognized pyrogenic "pro-inflammatory" cytokines include interleukin-1, tumor necrosis factor alpha, and interferon gamma. Regulation of cytokine secretion is very complex with many interactions between individual molecules and classes of molecules. The initial cytokine mediated rise of core temperature is only one facet of the febrile response. Other physiologic changes which are together called the acute phase response are somnolence, anorexia, changes in plasma proteins, altered synthesis of the hormones ACTH, glucagon, insulin, cortisol, catecholamines, growth hormone, TSH, thyroxin, aldosterone and vasopressin. Hematologic alterations include changes in leukocytes, lymphocytes, platelets and decreased red blood cell formation. Many acute phase proteins are secreted during the febrile response, some of which play a role in modulating inflammation and tissue repair. Pyrogenic cytokines act upon the preoptic region of the anterior hypothalamus of the central nervous system and upon peripheral tissues through specific receptors and pathways which are not yet delineated to produce changes in body temperature and also to limit the height of the fever rise. Thermoregulatory neurons involved in the febrile response are known to be completely inhibited at 41 to 42 C (105.8 to 107.6 F), the ceiling of the natural febrile range. Pyrogenic cytokines are balanced or "braked" by anti-inflammatory cytokines, arginine vasopressin, hypothermic neurochemicals, hypothermic peptides and even some of their shed soluble receptors. Thus, there is a complex and changing interplay of factors influencing the thermoregulatory set-point which causes it to change frequently resulting in the frequent changes in body temperature characteristic of most fevers.

Patterns of Fever: In the febrile state, the temperature is not controlled as tightly as the 0.5 degree C (0.9 degree F) variation that normal adults show during the day. There are several patterns of fever, some of which are associated with particular disease processes. Intermittent fevers are characterized by temperature patterns which dip into the normal range one or more times per day. Remittent fevers demonstrate wide swings in temperature but always remain above 38 (100.4). Hectic or "septic" or "high spiking" fevers show wide swings between highs and lows and may be either intermittent or remittent depending upon whether the low is in the normal range. Sustained fevers have temperatures that are always in the febrile range but vary less than 0.5 C (1 F). Relapsing fevers are recurrent over days to weeks. The pattern of fever has some value in diagnosis although exceptions to the associations are very common. Intermittent fever is associated with the systemic form of juvenile rheumatoid arthritis (Still's disease), miliary tuberculosis, mixed malarial infections, and may be produced with antipyretic therapy. Remittent fevers are associated with many viral infections, acute rheumatic fever, endocarditis with lower grade pathogens and Kawasaki syndrome. Hectic fevers suggest bacterial septicemia, endocarditis with high grade pathogens, occult or deep tissue abscesses, peritonitis, toxic shock syndrome and Kawasaki syndrome. Sustained fevers are associated with typhoid fever, nosocomial infection of devices such as intravenous lines and cerebral spinal fluid shunts. Relapsing fevers are characteristic of malaria, dengue, brucellosis and rat-bite fever.

Knowledge of the patterns of fever is useful in documentation and in describing the patient to others. It is sometimes of value in diagnosis and prognosis. It is important not to describe a patient as "afebrile" unless the temperature is in the normal range for at least an entire 24 hour period. Afebrile literally describes a patient with the "absence of fever," not just a patient whose temperature has briefly fallen into the normal range before it rises again. It is also imprecise to describe a "spiking fever" or a fever "spike" unless the temperature rises several degrees in a short period of time such as 4 hours or less.

Height of Fever and Response to Antipyretics: There is a weak correlation between height of fever and the severity of infection or whether it is viral or bacterial. However, this correlation is so weak that it is not clinically useful, because there is too much overlap between the viral and bacterial infection groups. The overwhelming majority of high fevers are caused by viral agents. Some highly lethal infections such as gram-negative bacterial septicemia may have only modest fever or even, most ominously, hypothermia. Conversely, the very benign and universal Human Herpesvirus (HHV) 6 and 7 or roseola infantum infections are characterized by fevers near the febrile ceiling, 40.5 C (104.9 F) or greater. There is a slightly increased likelihood (from about 4% to 8%) of occult bacteremia in young (6-18 months) children with temperatures over 40.0 C (104 F). However the overwhelming majority of children with high fever have non focal and presumed viral infections. Whether viral or bacterial, serious or trivial, five prospective studies in children have shown that temperature elevations had the same degree of response to antipyretic therapy (14-18). Therefore response or lack of temperature response to antipyretics usually does not distinguish between viral or bacterial infection or between trivial or serious infection. The child's clinical appearance, especially his level of alertness and appropriate social behavior, does help in determining if serious illness is present. Children with severe bacteremic infection still appeared clinically ill after successful fever reduction while the clinical appearance of children with

non-severe infections improved (18). Thus the focus for parents and physicians should be on the child's appearance and behavior, not the height of the fever or presence or absence of response to antipyretics.

A temperature rise is accomplished by increasing heat generation primarily through shivering and decreasing heat dissipation by shunting blood away from the skin surface. Non-shivering thermogenesis is accomplished through many other metabolic processes especially those in brown fat. Patients with a rising temperature are hyperalert, feel jumpy or jittery, complain of cold sensations and have shivering, chills or violent rigors. Temperature lowering is associated with increased heat dissipation at the skin surface with dilatation of surface vessels and sweating which causes further evaporative cooling. Patients feel hot and have profound lassitude which inhibits muscle activity and prevents heat generation. These states alternate as the body temperature rises and falls. The rate at which the temperature changes determines the severity of these symptoms. Chills and shivering are increased and made much more uncomfortable if external cooling is applied.

Is fever harmful? To date there is no clear evidence that fever causes harm to the host. Temperatures of up to 41.5 C (106.7 F) are tolerated without any reported evidence of damage to the brain or other organs (19). Temperature elevations higher than this are not caused by response to an infecting agent but are usually associated with profound failure of thermoregulation such as exposure to extreme heat (heat stroke), severe brain injury with damage to the thermoregulatory center, and adverse reactions to anesthetics or neuroleptic drugs (malignant hyperthermia). There are no reports of brain damage caused by fever as a response to infection in a previously normal individual. Concerns have been expressed that fever may pose an increased stress in seriously ill individuals by increasing metabolic activity, heart rate, and respiratory rate. There is little evidence on this point. One large placebo controlled study of febrile adult ICU patients demonstrated that ibuprofen reduced fever and metabolic rate but had no beneficial effect on survival (20).

Is fever beneficial? There is limited evidence that fever is beneficial. Some animal infection studies have demonstrated a direct association between fever and survival (21-25). Other animal model infection studies demonstrated an increase in mortality if fever was suppressed with antipyretics (26-28). These types of studies have flaws which reduce their applicability to humans especially because some are done in cold blooded animals, some induce elevated temperature with external warming and some use uncommon pathogens. Some studies of patients with severe bacterial infections have shown a direct positive correlation between height of fever and survival (29-34). A controlled study in children with varicella demonstrated both a shorter duration of fever and more rapid healing of lesions in placebo recipients than those treated with acetaminophen. The magnitude of the effect was approximately equal to the effect of antiviral therapy on varicella (35). Two common cold studies showed more severe respiratory symptoms and longer duration of rhinovirus shedding when fever was suppressed with aspirin or acetaminophen (36,37).

Should Fever be treated with Antipyretics? Current clinical practice is that fever reducing drugs are employed routinely, often before any investigation as to the nature or cause of the fever is carried out. The rationale supporting this practice is that it is harmless and increases patient comfort. Indeed, antipyretics are often requested for and given to patients who are perfectly comfortable and have very modest temperature elevation. Patients often initiate antipyretic therapy on their own without medical consultation. It would be unreasonable to seek medical evaluation for all fevers so some degree of discretion needs to be permitted to patients. Some precautions need to be considered when recommending routine antipyretic treatment:

1. Aspirin therapy for fevers of varicella and influenza caused an epidemic of life-threatening Reye's Syndrome.
2. Acetaminophen is an extraordinarily safe drug within its dosing range. However, fatal liver damage from unintentional overdose of acetaminophen for fever has been reported.
3. Case control studies indicate that treatment of the fever of streptococcal toxic shock syndrome with ibuprofen is associated with increased mortality (38-39).
4. Ibuprofen causes platelet inhibition and upon occasion, significant gastrointestinal hemorrhage. Routine use of ibuprofen amplifies this risk.

If patients appear to be very uncomfortable from fever, it is reasonable to administer antipyretics. Antipyretic therapy may also be useful in a febrile child who appears slightly ill with a non-focal examination suggesting a benign illness. The administration of antipyretics with temperature normalization may result in improvement of the patient's behavior and appearance, thus avoiding unnecessary laboratory testing, antibiotics or hospitalization.

Another rationale for the routine use of antipyretic therapy in children under 5 years is that it will reduce the likelihood of febrile seizures. Many febrile seizures occur early in the course of illness with the seizure being the first sign that the child is febrile. In these cases, there is no opportunity for antipyretics to lower the temperature. A study of children with a history of febrile seizures found the recurrent seizure rate to be 5% in children treated with phenobarbital and antipyretics while 25% of those treated with placebo and antipyretics had a recurrent seizure (40). Two placebo controlled studies using standard and high dose acetaminophen during fever failed to show a benefit for the active drug in preventing seizure recurrence (41,42). We have no way of determining which normal child will be affected, but all children do not appear to be at equal risk for febrile seizures. Only 2% of children ever have a seizure while exposure to high body temperature is virtually universal by age 5 years. Although the literature fails to provide evidence that antipyretic therapy prevents recurrent febrile seizures, these seizures are very emotionally distressing to parents. Parents may feel more comfortable if antipyretic therapy is employed. When seizures occur despite appropriate use of antipyretics, parents should be counseled that they did all that was appropriate so that they will not employ excessive treatment with the next febrile illness or suffer unnecessary grief.

Approach to the febrile child: There are several clinical decision rules that are commonly employed in pediatric practice. Following these decision rules constitutes a conservative approach. Highly experienced clinicians may be able to identify low risk individuals who may fit the decision rule, but are unlikely to benefit from their recommendations.

Fever in infants under 8 weeks of age: This generally prompts a sepsis work-up consisting of a CBC, blood culture, catheterized urine culture, urinalysis, chest X-ray (if respiratory symptoms are present), and lumbar puncture. Empiric antibiotics and hospitalization are recommended routinely for this age group; however, children in the 4 to 8 week range have been treated as outpatient in some patient series if the following conditions are met: 1) the sepsis work-up is negative, 2) empiric antibiotics (e.g., ceftriaxone) are given, 3) the infant is feeding well, is not fussy and appears well clinically, 4) parents are assessed to be reliable observers, and 5) a source of reliable primary care is identified. A positive RSV ELISA may be considered to be the source of the fever which would make the infant less likely to benefit from the urine and cerebrospinal fluid studies, however, hospitalization may still be necessary.

Occult urinary tract infection: UTI may be difficult to diagnose in young children. Girls under 24 months of age and boys under 6 months of age with temperatures greater than 39 degrees C (102.2 F) are at modest risk for UTI. Most experts have recommended catheterized urine cultures for this group. Uncircumcised males are at a higher risk (although the magnitude of this additional risk is controversial). Some experts have recommended that uncircumcised boys be checked for UTI up until 24 months of age. Some children

in this age group present with predominant respiratory symptoms (e.g., bronchiolitis), which point to a respiratory source of the fever. One study demonstrated that such patients are at reduced risk for UTI, but it still occurs, therefore urine testing may still be valid even for those with respiratory symptoms (43).

Occult bacteremia: Children from 3 months to 36 months of age with a temperature greater than 39 degrees C (102.2 F) are at risk for occult bacteremia. The risk of this is less than 4% and most cases, result in spontaneous resolution, even without antibiotic therapy. The risk of occult bacteremia is further modified by H. influenzae vaccine, pneumococcal vaccine, age and other factors making this decision complex and the management options controversial.

Otitis media is often diagnosed in febrile children, but it is likely that most cases of otitis media cause only mild degrees of fever. Thus, assuming that a diagnosis of otitis media accounts for the fever, may result in missing a UTI. Although antibiotic treatment for otitis media will frequently treat the UTI as well, if a vesicourinary anomaly is responsible for the UTI, then the patient will be at risk for subsequent recurrent pyelonephritis in the future until the vesicourinary anomaly is identified.

The utility of routine CBCs to identify septic patients has been studied extensively. Because of the excessive overlap of WBC results, CBCs are only occasionally indicative of a serious condition and generally not helpful in identifying septic patients. Clinical appearance (does the child appear to be toxic, lethargic, excessively irritable, or very ill appearing) is the most reliable clinical predictor of sepsis after 2 to 3 months of age.

Fever is a complex and highly regulated host response to a microbial or inflammatory stimulus. Fever is most often related to infection but is also seen prominently in auto-immune and neoplastic disease. Controlling fever should not be a major objective in itself. Although fever is often uncomfortable, it is not medically harmful to the host and may be beneficial. With that in mind we can now answer our mother and the nurse's concerns outlined in the vignette which introduced this chapter. Her son will not become brain-damaged as a result of his fever which is a natural and possibly helpful response to an as yet undiagnosed infection. It is unlikely that her son will have a seizure or "go into convulsions" both because it is statistically unlikely and because he has been febrile for several hours without having had a seizure. His fever will not continue to rise much as he has already approached the natural ceiling for the febrile response. It is more important at this point to assess the cause of the fever with a physical examination and any diagnostic testing which may be indicated, rather than to administer antipyretics. Drastic external cooling measures such as a cooling blanket or a cold water bath are absolutely not indicated and will certainly make the child feel worse (44). He should not be given another dose of acetaminophen as he has already received double doses. His mother must be told that giving more acetaminophen than indicated in future illnesses could cause liver damage. Acetaminophen and ibuprofen appear to be equally effective and safe in fever reduction in children (45,46). There is no reported clinical trial of the safety and efficacy of combining these agents in the symptomatic treatment of fever in children. Since our patient does not appear to be uncomfortable, it is not necessary to give him ibuprofen at this time. Simply dressing him minimally and offering him extra fluids without expecting him to eat solid foods is all that is required for fever treatment. Since he has a normal physical examination and has been previously immunized with Haemophilus influenzae b and pneumococcal conjugate vaccines, he is at very low risk for serious bacterial infection. Once his underlying illness has been fully addressed, ibuprofen therapy may be offered if he appears uncomfortable. It should be stressed that antipyretic therapy is entirely optional and should be given only if he needs relief of noxious fever related symptoms. Given his normal physical exam and age appropriate behavior, he most likely has an HHV 6 or 7 roseola related illness. Considering all that is known about temperature regulation in the febrile response, the control of the typically high fever characteristic of this illness rests more with the patient's physiology than with the influence of his mother or the medical profession. In evaluating any patient with fever it is of paramount importance to remember that fever is a sign of disease and not the disease process itself.

Notes:
Acetaminophen is generically also called APAP (abbreviation) and paracetamol (other countries).
The formula to convert degrees F to degrees C is TempC = (TempF - 32)/1.8
The formula to convert degrees C to degrees F is TempF = (TempC X 1.8) + 32

Questions

1. True/False: Defining an elevated temperature is difficult and variable because the "normal" core temperature is not a fixed value, and the methods of measuring temperature have varying degrees of accuracy.

2. Which of the following is true?
   a. Treating fever with antipyretics is clearly harmful and should be always discouraged.
   b. Treating fever with antipyretics is clearly beneficial, without adverse effects and should always be recommended.
   c. Treating fever with antipyretics is optional.
   d. None of the above.

3. True/False: Temperatures above 40 degrees C (104 F) result in febrile seizures in most patients.

4. True/False: Ibuprofen has a superior antipyretic effect compared to acetaminophen.

5. Febrile children at risk for occult urinary tract infection include those with a temperature above 39 degrees C. What is the commonly used age ceiling for boys and for girls?

6. True/False: Teething is known to cause fever.

7. True/False: The diagnosis of acute otitis media is a reliable explanation for a high fever, thus eliminating the need to for other diagnostic considerations in a patient with an otherwise benign examination.

8. True/False: High fever may cause brain damage.

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Answers to questions
1. True
2. c
3. False
4. False
5. 6 months for boys, 24 months for girls.
6. False. At the most, teething might causes a very slight temperature elevation.
7. False. Otitis media is not considered to be a reliable source of causing a high fever. Other conditions, such as UTI, need to be considered.
8. False.

Chapter VI.4. Inhibitory and Bactericidal Principles (MIC & MBC)

Loren G. Yamamoto, MD, MPH, MBA

A 7 year old male presents to his physician's office with thigh pain and fever since yesterday afternoon. He has a minimal limp and no history of trauma.

Exam VS T37.5, HR 90, RR 18, BP 110/70. He is alert and not toxic. His exam findings are only positive for tenderness in his mid femur region. His hip exam is normal. He has no skin sores, bruises or other areas of tenderness. His gait appears to be normal except for an occasional suggestion of a limp.

Plain radiographs of his femur and hip are normal. His CRP and ESR are high so a bone scan is obtained that afternoon which shows a hot spot in his mid femur. He is hospitalized for acute osteomyelitis. He is initially treated with IV vancomycin. An orthopedic procedure is performed to drain some pus and to obtain a culture and biopsy. On hospital day 3, his clinical condition is improved. Cultures of his blood and the bone aspirate grow Staph aureus which is sensitive to cephalosporins and methicillin. His antibiotics are changed to IV oxacillin. He continues to improve. Consultants recommend that he be treated for 6 weeks with IV antibiotics. His medical insurance company approves inpatient antibiotics for 7 days and requests that the remainder of his antibiotics be administered as an outpatient. Is there a rational method to provide him with inpatient levels of antibiotics as an outpatient?

Each bacteria has a level of antibiotic which will inhibit growth but not kill the organisms. This is called the minimum inhibitory concentration (MIC). Related to this, a higher antibiotic concentration will kill the organisms. This is called the minimum bactericidal concentration (MBC). By understanding the concepts in determining antibiotic concentrations compared to the MIC and MBC, we can make rational decisions in determining how successful antibiotic treatment is likely to be.

Pharmacologists have taught us that some antibiotics are "bactericidal" and some are "bacteriostatic". These terms are slight misnomers since all antibiotics are potentially bactericidal and bacteriostatic at different concentrations. The "bactericidal" and "bacteriostatic" terminology originates from whether the antibiotic's mechanism is based on inhibiting cell wall formation ("bactericidal") or inhibiting bacterial metabolism or ribosomal protein synthesis ("bacteriostatic"). The idea is that if cell wall formation is blocked, the organisms will lyse and perish, but if metabolism or protein synthesis is blocked, the organisms merely slow down. While this is true to some degree, bactericidal or bacteriostatic outcomes are dependent on the concentration of the antibiotic as well. A low dose of a "bactericidal" antibiotic may only inhibit bacterial growth, while a high dose of a "bacteriostatic" antibiotic will be bactericidal. Additionally, organisms which are not proliferating may not be significantly affected by anti-cell wall antibiotics, in which case anti-ribosomal antibiotics would be more effective.

An example of this is the effect of bug spray on a cockroach. A light spray will only slow the cockroach down (a cockroach-static level). By tomorrow, the cockroach will recover. However, if one drowns the cockroach in bug spray (a cockroach-cidal level), the cockroach will perish.

Modern laboratory methods can rapidly determine the MIC and MBC for cultured organisms for multiple antibiotics simultaneously. However, to understand this better, the following clinical example will be used to demonstrate these concepts. Refer to the table below:

Tube	Antibiotic Concentration	Day 2	Day 4
1	10.0	Clear	Clear
2	5.0	Clear	Clear
3	2.0	Clear	Turbid
4	1.0	Clear	Turbid
5	0.5	Turbid	------
6	0.2	Turbid	------

The table above is an example which describes the result of MIC/MBC determinations for an organism from our patient with a hypothetical antibiotic. There are six tubes with varying concentrations of antibiotic in a bacterial culture broth. Tube 1 contains the highest concentration of antibiotic and tube 6 contains the lowest concentration of antibiotic. The organism is inoculated into all 6 tubes. After a 2 day incubation, the first 4 tubes are clear (which indicates that the organisms did not grow in these tubes). Tubes 5 and 6 are turbid due to bacterial growth which means that an antibiotic concentration of 0.5 is neither inhibitory nor bactericidal.

For tubes 1, 2, 3 and 4, it is not known whether the organisms present in these tubes have died (bactericidal concentration) or their growth is merely inhibited (inhibitory concentration). These tubes contain either dead organisms or viable growth-inhibited organisms. The next step is to centrifuge tubes 1 through 4. All solid debris (dead or alive organisms) will be centrifuged to the bottom of the tube. After centrifugation, the supernatant containing the antibiotic is poured off. Fresh broth without antibiotic is now added to the tubes. After another two days of incubation (on day 4), tubes 1 and 2 are clear, while tubes 3 and 4 are turbid. This means that tubes 3 and 4 contained viable organisms which were inhibited by the antibiotic, but now that the antibiotic is gone, they are able to grow. Tubes 1 and 2 are still clear which means that all organisms in these tubes were killed. Thus tubes 3 and 4 contain inhibitory concentrations of antibiotic, while tubes 1 and 2 contain bactericidal concentrations of antibiotic. Thus, the minimum inhibitory concentration (MIC) of this organism for this antibiotic is 1.0 (tube 4), while the minimum bactericidal concentration (MBC) of this organism for this antibiotic is 5.0 (tube 2).

Now that we know the MIC and MBC for this organism and this antibiotic, we can put the patient on oral antibiotics and see what antibiotic levels can be achieved in the patient's bloodstream. We could measure an antibiotic level 1-2 hours after an antibiotic dose is given (peak level) and one hour before the next antibiotic dose is given (trough level). At a minimum, the tough level should be above the MIC and the peak level should be above the MBC. In practice, the peak level should be several times higher (e.g., 8 times higher) than the MBC, depending on the type of infection. If such levels cannot be obtained by oral antibiotics, then IV antibiotics must be maintained for the duration of therapy.

Most clinical laboratories are not able to measure levels of all antibiotics. For example, a clindamycin or a trimethoprim/sulfamethoxazole level may not be available. If preliminary sensitivity testing shows drug sensitivities to such antibiotics, a different method may be necessary to determine if satisfactory MICs and MBCs can be obtained with these antibiotics. This is called the Schlichter test, which is demonstrated in the example below:

Peak Tube	Peak serum Dilution	Day 2	Day 4
1	1:2	Clear	Clear
2	1:4	Clear	Clear
3	1:8	Clear	Clear
4	1:16	Clear	Turbid
5	1:32	Clear	Turbid
6	1:64	Turbid	------

Trough Tube	Peak serum Dilution	Day 2	Day 4
A	1:2	Clear	Clear
B	1:4	Clear	Clear
C	1:8	Clear	Turbid
D	1:16	Clear	Turbid
E	1:32	Turbid	------
F	1:64	Turbid	------

The tables above are an example which describes the result of MIC/MBC determinations for an organism from our patient with a hypothetical antibiotic for which, antibiotic levels are not routinely available in the clinical lab. There are six tubes with varying dilutions of the patient's serum mixed with culture broth. Tubes 1-6 are drawn just after the patient receives an antibiotic dose (peak level). Tubes A-F are drawn just before the patient receives an antibiotic dose (trough level). Tube 1 contains the highest concentration of antibiotic for the peak levels. Tube A contains the highest concentration of antibiotic for the trough levels.

The organism is inoculated into all 6 tubes for peak and tough. After two days of incubation, tube 6 is turbid for the peak tubes, and tubes E and F are turbid for the trough tubes. For these turbid tubes, we know that active bacterial growth has taken place so these dilutions are neither inhibitory nor bactericidal.

For tubes 1, 2, 3, 4, 5 for the peak tubes, and tubes A, B, C, D for the trough tubes, it is not known whether the organisms present in these tubes have died (bactericidal concentration) or their growth is merely inhibited (inhibitory concentration). These tubes contain either dead organisms or viable growth-inhibited organisms. The next step is to centrifuge tubes 1, 2, 3, 4, 5 for the peak tubes, and tubes A, B, C, D for the trough tubes. All solid debris (dead or alive organisms plus some blood cells) will be centrifuged to the bottom of the tube.

After centrifugation, the supernatant containing the antibiotic (from the patient's serum) is poured off. Fresh broth without antibiotic is now added to the tubes.

For the peak and trough tubes, after another two days of incubation (on day 4), tubes 1, 2, 3, A, B are clear, while tubes 4, 5, C, D are turbid. This means that turbid tubes 4, 5, C, D contained viable organisms which were inhibited by the antibiotic (in the patient's serum), but now that the antibiotic is gone, they are able to grow. Tubes 1, 2, 4, A and B are still clear which means that all organisms in these tubes were killed. Thus tubes 4, 5, C and D contain inhibitory concentrations of antibiotic, while tubes 1, 2, 3, A and B contain bactericidal concentrations of antibiotic. Thus, the minimum inhibitory concentration (MIC) of this organism for this antibiotic is occurs at a 1:32 dilution (tube 5) at peak antibiotic levels, and 1:16 dilution (tube D) at trough antibiotic levels, while the minimum bactericidal concentration (MBC) of this organism for this antibiotic is 1:8 dilution (tube 3) at peak antibiotic levels, and 1:4 dilution (B) at trough antibiotic levels.

What does this mean? This data tells us that the antibiotic blood levels exceed the MBC 4 to 8 times from trough to peak. This is excellent. However, for an infection such as osteomyelitis, bone levels are not necessarily the same as blood levels. Thus, blood levels well in excess of MBC and MIC are desirable. If such levels can be demonstrated with oral antibiotics using these tests, then the patient can be treated with oral antibiotics as an outpatient, and therapeutic success is more certain. Thus our patient does not need to remain in the hospital for 6 weeks of IV antibiotics. He can be discharged and take antibiotics at home. This is much less costly and it should be just as effective as long as the patient is compliant.

The utilization of MIC/MBC data and the Schlichter test is complex and controversial. The most common infections which require very long antibiotic courses (4 to 6 weeks) are bone and joint infections (osteomyelitis and septic arthritis) and bacterial endocarditis. While still controversial, peak drug levels 8 times the MBC are felt to be the minimum levels to predict therapeutic success for these infections. Peak levels below this may be insufficient. In general, higher levels are better, and some organisms typically require higher levels than other organisms.

Questions

1. How does a bacteriostatic antibiotic behave in a bactericidal fashion?
2. How does a bactericidal antibiotic behave in a bacteriostatic fashion?
3. Do all infections require MIC/MBC or Schlichter tests? Why or why not?
4. When should a Schlichter test be performed?
5. When is it NOT possible to perform MIC/MBC determination testing?
6. If the infection is in bone (osteomyelitis), in joint fluid (septic arthritis), in urine (UTI), or in any body space, how can we be sure that adequate antibiotic levels are obtained if we are only able to measure MIC/MBC in the blood?

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Answers to questions

1. When the level of the antibiotic is so high that all organisms are killed.
2. When the level of the antibiotic is so low that organism growth is inhibited, but they are not killed.
3. No. MIC/MBC or Schlichter tests are only useful when a very long course of antibiotics are anticipated and the patient must be changed to oral antibiotics to complete the antibiotic course as an outpatient. These tests are necessary to determine if it is possible to attain sufficient blood levels with the oral antibiotics to predict therapeutic success. The most common clinical scenarios would be for osteomyelitis, septic arthritis and bacterial endocarditis.
4. A Schlichter test should be performed when the lab is unable to measure levels of the antibiotic that is to be used.
5. When we don't have an organism (cultures are negative).
6. We are never totally sure. We do know that compared to blood levels, most antibiotics have lower levels in bone and in joint fluid, but higher levels in urine.

Chapter VI.5. Antibiotics
Loren G. Yamamoto, MD, MPH, MBA

A 7 year old presents to the emergency department with fever and an expanding area of redness over his left calf. He has had fever for only 8 hours with a maximum temperature of 39 degrees C. He had a bug bite on his left calf three days ago. It now appears to be infected and painful. There is no pus, but overnight, there is a large area of redness noted with slight swelling. Because of these symptoms, he is brought to the emergency room.

Exam VS T 38.5, HR 90, RR 24, BP 100/65. He is alert and not toxic. His HEENT, heart, lung and abdominal exam findings are unremarkable. His left lower extremity is negative for any lymphangitis or lymphadenopathy. There is a 6 by 12 cm oval region of erythroderma with a sharply demarcated border over his mid lateral calf. There is a central skin sore which does not appear to excessively swollen. There is no fluctuance or drainage. There is mild tenderness within the red region. There is no bony tenderness and he is able to ambulate normal.

A culture of the central skin lesion is obtained. A blood culture is also obtained. He is given a dose of IV clindamycin and he is prescribed a course of oral clindamycin. His conditions improves the next day. His skin sore culture grows beta hemolytic group A streptococci. His blood culture is negative. His antibiotic treatment is changed to penicillin and he has a full recovery.

Antibiotics are one of the most important classes of medications prescribed by physicians. When you consider the major classes of pharmacologic agents which are used to treat children, you will find that there are only a few classes of drugs which are used frequently. These include antipyretic/analgesics, antibiotics, bronchodilators and a few others which are less common such as corticosteroids, anesthetics, cardiac medications, etc. Thus, out of the three large classes of drugs which are frequently used for children, antibiotics are a major group. Proper antibiotic prescribing is an important medical practice skill.

The most important item of information is to be able to use an antibiotic which satisfactorily cures the patient of an infection. While the mechanism of action of the different antibiotics are important, this is not as important in most instances. Antibiotic therapy is initiated in three basic ways: 1) empiric therapy, 2) specific therapy, 3) prophylaxis.

Empiric therapy is the selection of treatment based on clinical and laboratory information with the exception of culture and sensitivity information. Specific therapy is the selection of an antibiotic based on the culture and sensitivity testing of the organism causing the infection. Prophylaxis is the use of antibiotics to prevent an infection which is anticipated.

Empiric therapy is based on a three step process: 1) identifying a clinical entity, 2) knowing which organisms cause this entity, 3) selecting an antibiotic which covers these organisms. Some physicians use a two step process which is to identify the clinical entity, then select an antibiotic which is commonly used for this entity. I would prefer that students and physicians in training learn the three step process because it is a deeper level of understanding. The three step method is a universal approach which will always work as the future challenges us with changes in antimicrobial resistance patterns, newly developed antibiotics, insurance company drug coverage restrictions, side effect profiles, allergies, compliance issues, etc. The two step process is similar to following a cook book without understanding it.

Many students have learned simple rules to select antibiotics. Unfortunately, simple rules usually DO NOT work. A commonly taught rule is that penicillins and cephalosporins (which inhibit peptidoglycan synthesis) work for gram positive organisms, while aminoglycosides (which inhibit bacterial ribosome function) work for gram negative organisms. This is often true, but it is an oversimplification which has too many exceptions for this rule to be useful. This rule is based on the premise that gram positive organisms are more dependent on peptidoglycan cell wall synthesis (that's why they stain gram positive), while gram negative organisms are not as dependent on peptidoglycan cell wall synthesis. Staphylococcus aureus is a gram positive organism which is highly resistant to penicillin. Staph aureus is usually sensitive to penicillinase resistant penicillins and cephalosporins, but resistance to these is becoming more frequent (25% or more). Aminoglycosides such as gentamicin cover Staph aureus with a much higher frequency than cephalosporins. Neisseria gonorrhoeae is a gram negative organism for which the treatment of choice is ceftriaxone. Neisseria gonorrhoeae used to be treated with penicillin, but the emergence of PPNG (penicillinase producing Neisseria gonorrhoeae) has rendered penicillin ineffective. Staphylococcus epidermidis is a gram positive organism which is highly resistant to penicillins and cephalosporins. Staph epi must generally be treated with vancomycin.

Are there any simple rules which work? Unfortunately, no. However, it is a certainty that antibiotic resistance patterns will change and new antibiotics will be developed. The best way to learn the three step process is to do it frequently. If you do it again and again, it will become routine and relatively easy.

Empiric therapy is generally used first. Handbooks on antimicrobial therapy are commonly available. Such a handbook will provide useful information in learning the three step process. Most handbooks have three separate listings:

1. A list of clinical infections and most commonly used antibiotics for these infections.
2. A list of clinical infections and the common organisms which cause these infections.
3. A list of organisms and their usual sensitivity and resistance patterns (this is often a table). Similarly, most hospitals publish annual sensitivity and resistance percentages of the organisms which have been cultured in the clinical laboratory. These hospital results would be the most current and community specific sensitivity and resistance patterns for the organisms that are likely to be affecting your patients.

The first listing (#1 above) is the two step method of selecting antibiotics. Once a clinical entity is identified, then an antibiotic from this listing can be selected.

Items #2 and #3 above, are necessary for the three step method. Although this may seem a longer process at first, it will provide students and physicians in training with a better understanding of antibiotic use. After utilizing the three step method frequently, you will become very good at this, and most antibiotic decisions in the future will not require the assistance of a handbook, The three step process described below:

Step 1. Identification of a clinical entity. A history and examination provides clinical information. Sometimes laboratory and imaging information may also be necessary to add more certainty to a diagnosis. Such an entity may be cellulitis, otitis media, pneumonia, osteomyelitis, gastroenteritis, pelvic inflammatory disease, urinary tract infection, rule out sepsis, etc.

Step 2. What organisms cause this entity? For an entity such as cellulitis, we know that the most common organisms are group A streptococci and staphylococcus aureus.

Step 3. Select an antibiotic which covers the organisms which are potentially causing the infection. Group A strep is sensitive to all penicillins and cephalosporins. Staph aureus is usually sensitive to cephalosporins and penicillinase resistant penicillins such as oxacillin and cloxacillin. However, there is growing staph aureus resistance to these drugs (currently about 25% or more). Staph aureus is about 95% sensitive to clindamycin and this also covers group A strep. Thus, clindamycin appears to be the best choice to treat cellulitis in this instance. Another consideration is the severity of the infection. For a life threatening infection such as bacterial meningitis, there must be the certainty of 100% coverage. Thus, initial broad spectrum or multiple antibiotics may need to be used empirically. As opposed to a less serious infection such as otitis media or impetigo, in which case 80% coverage certainty may be sufficient.

It is possible to stratify this further. A more experienced physician examines the cellulitis and indicates that this cellulitis is caused by group A strep which more commonly causes large areas of erythroderma surrounding a single skin sore. Staph aureus cellulitis is usually associated with suppuration and a smaller area of redness and induration surrounding a central abscess. Thus, clinically, one could be more certain that this is a group A strep cellulitis which can be treated with penicillin. In the case, the patient was initially treated with IV clindamycin because high antibiotic levels are immediately achieved to be followed by a course of oral clindamycin. When the results of the culture returned identifying the organism and its sensitivity to penicillin, the patient could then be changed to specific therapy with penicillin.

Specific therapy utilizes culture and sensitivity information which is usually available 1 to 3 days later. The general principle is to select the antibiotic which is the most effective with the least side effects. Additionally, it may be preferable to select the antibiotic with the most narrow spectrum to reduce the likelihood of significantly altering the patient's normal flora. Sometimes, physicians may be limited by cost and compliance issues. For example, there may be two possible treatments; one which is B.I.D. costing $80 and another which is Q.I.D costing $10. One is less expensive, but it may be more difficult to ensure compliance. Such decisions are judgments which physicians must make in conjunction with patient preferences.

Prophylaxis is the utilization of antibiotics for an infection which is anticipated. An example would be a dog bite wound in which an infection is anticipated several days later. In addition to cleansing and irrigating the wound, antibiotics may be able to reduce the patient's risk of infection. Patients with vesicoureteral reflux are at greater risk for urinary tract infections. Thus, placing these patients on prophylactic antibiotics (usually once a day or twice a day) will reduce their likelihood of acquiring a UTI. Patients with rheumatic fever and subsequent rheumatic heart disease are at risk for worsening heart disease if another group A streptococcal infection is acquired. Thus, such patients are placed on daily oral penicillin or monthly long acting benzathine penicillin injections to prevent group A streptococcal infections.

New antibiotics will be developed in the future. As a preliminary discussion, antibiotics can be classified into 7 groups: penicillins, cephalosporins, aminoglycosides, sulfonamides, quinolones, macrolides and other.

Penicillins

Penicillins inhibit bacterial cell wall formation by inhibiting peptidoglycan synthesis. Penicillins can be further classified into three groups: penicillin, broad spectrum penicillins and anti-staph aureus penicillins. Penicillin typically covers group A and group B streptococci, most pneumococci, Neisseria meningitidis, Pasteurella multocida, Listeria and most anaerobes (with the exception of bacteroides fragilis). Broad spectrum penicillins include amoxicillin, ampicillin, carbenicillin, ticarcillin, piperacillin, azlocillin, mezlocillin, etc. This group covers more gram negative organisms such as E. coli, Proteus, Klebsiella, etc. With the exception of amoxicillin and ampicillin, the other broad spectrum penicillins cover pseudomonas as well. Broad spectrum penicillins can be combined with penicillinase inhibitors such as clavulanate and sulbactam. These combinations drug such as Augmentin (amoxicillin/clavulanate), Unasyn (ampicillin/sulbactam), Timentin (ticarcillin/clavulanate) and Zosyn (piperacillin/tazobactam) cover most staph aureus (but not MRSA) and other penicillinase producing organisms such as beta-lactamase producing Haemophilus influenzae B.

It should be noted that amoxicillin is metabolized to ampicillin in the bloodstream. Thus, these two antibiotics have identical coverage. Amoxicillin is better absorbed from the GI tract which is why amoxicillin should be favored via the PO route (except for GI infections) over ampicillin, and ampicillin should be favored via the IV route (amoxicillin is no longer available IV).

The anti-staph aureus penicillins are also called the penicillinase resistant penicillins which include methicillin, oxacillin, nafcillin, cloxacillin, dicloxacillin. These drugs are targeted against staph aureus which is why this group should more accurately called the anti-staph aureus penicillins. Methicillin resistant staph aureus (MRSA) is resistant to all the penicillins in this group. About 25% or more of staph aureus are currently MRSA. The term "penicillinase resistant penicillins" is a misnomer. It is true that staph aureus is penicillin resistant because of penicillinase production, but the term "penicillinase resistant penicillins" implies that they will cover all penicillinase producing organisms, but they do not cover penicillinase producing Neisseria gonorrhoeae, Haemophilus influenzae, Bacteroides fragilis, and many other penicillinase producing organisms. Thus, this group should be more appropriately called the anti-staph aureus penicillins, because the only penicillinase producing organism which they cover to a moderate degree is staph aureus.

Cephalosporins

Cephalosporins are structurally similar to penicillins with a similar mechanism of action. Cephalosporins are difficult to learn because there are many of them and new ones are frequently introduced. The "generation" of cephalosporins is only slightly helpful. In general, all cephalosporins cover all penicillin sensitive organisms with the exception of Listeria and Pasteurella. Coverage for group B streptococci is better with penicillin than with cephalosporins. Cephalosporins also cover many gram negative organisms such as E. coli, Klebsiella, Proteus, etc. Cephalosporins also cover staph aureus, but only to a similar degree as the anti-staph aureus penicillins (i.e., MRSA is cephalosporin resistant as well). Two generalizations that usually hold true are: 1) lower generations of cephalosporins cover staph and strep better than the higher generation cephalosporins (but staph and strep coverage with high generation cephalosporins is still generally adequate), and 2) higher generations of cephalosporins have extended coverage of gram negative organisms. Unfortunately, the "generation" of cephalosporins does not provide clinicians with specific properties which permit us to use any drug in the same generation. Within the higher generations, each cephalosporin has specific properties which make one more useful than others. In my view, using the generation of the cephalosporin is NOT the best way to learn how to use cephalosporins. The best way to select cephalosporins, is to learn the properties of a single first generation cephalosporin, then find other useful clinical properties of another cephalosporin which provides clinicians with a useful clinical advantage. If a cephalosporin has no clinically useful advantages which separate it from other cephalosporins, then we should purge it from our memory.

The prototype first generation cephalosporin is cefazolin (Kefzol and Ancef are trade names), which is for IV use. Cephalexin (Keflex trade name) is an oral first generation cephalosporin with an essentially identical spectrum. These drugs have the basic cephalosporin coverage described above.

What if we needed coverage for anaerobes? Then we would use IV cefotetan (Cefotan) or cefoxitin (Mefoxin), since these cephalosporins cover most anaerobes (but not 100%). Thus, these cephalosporins would be preferred for appendectomy prophylaxis.

What if we needed Haemophilus influenzae or Moraxella catarrhalis coverage? Then we would use IV cefuroxime (Zinacef), cefotaxime (Claforan) or ceftriaxone (Rocephin). We could also use oral cefuroxime (Ceftin) or cefaclor (Ceclor).

What if we needed to cover meningitis? We need the additional property of penetration through the blood brain barrier into the CNS and CSF. Although cefuroxime covers all the meningitis organisms, it does NOT penetrate the blood brain barrier as well as cefotaxime and ceftriaxone, therefore, one of these two latter drugs would be preferable.

What if we needed pseudomonas coverage? Then we would use ceftazidime (Fortaz) since this is one of the few cephalosporins with pseudomonas coverage.

What if we wanted to treat an infection as an outpatient, but we wanted to be certain that high antibiotic levels would be maintained for at least 24 hours (similar to an over night hospitalization for IV antibiotics)? Then we would use ceftriaxone (Rocephin) since it has a long half-life and its usual dosing interval is every 12 to 24 hours. Thus, giving a single dose of IM or IV ceftriaxone, results in antibiotic levels which would be similar to an overnight hospitalization with IV antibiotics, at a substantially lower cost since it can be done as an outpatient.

Thus, as a simplification, the only IV cephalosporins we need to know for pediatrics are cefazolin (first generation), cefotetan (better anaerobe coverage), ceftriaxone (extended coverage which includes Haemophilus influenzae and Moraxella, good blood brain barrier penetration, and a long duration of action), and ceftazidime (pseudomonas coverage). The only oral cephalosporins we need to know are cephalexin (first generation), cefuroxime (extended coverage) and perhaps cefixime (once a day dosing often recommended for UTI). Other cephalosporins are less important. We will still be exposed to them, because other physicians will prescribe them, and there are additional subtle factors which may slightly favor other cephalosporins. But for most clinical applications, the above will suffice.

Aminoglycosides

Aminoglycosides inhibit bacterial ribosomal function. Aminoglycosides are more toxic than penicillins and cephalosporins. Thus, they must be maintained within a certain therapeutic range. At high levels, aminoglycosides are nephrotoxic and ototoxic. These drugs are also weak neuromuscular blocking agents so they can cause respiratory depression or apnea if given in to a patient with neuromuscular compromise (e.g., early infant botulism, Guillain Barre syndrome, severe myopathies, etc.).

Aminoglycosides are generally directed at gram negative organisms (especially the Enterobacteriacae, also known as stool germs). However, aminoglycosides also cover gram positive organisms such as Staph aureus and many streptococci. In fact, while Staph aureus may be 25% resistant to the anti-staph aureus penicillins and cephalosporins, Staph aureus resistance to aminoglycosides is 10% or less.

Gentamicin is the most basic aminoglycoside. Other aminoglycosides with extended coverage include tobramycin and amikacin. Note the spelling of Gentamicin compared to tobramycin. The difference is the "micin" (no "y"). Gentamicin is commonly misspelled. Tobramycin and amikacin have extended gram negative coverage which includes most pseudomonas.

Sulfonamides

Most sulfonamides inhibit various steps in metabolic pathways such as those which inhibit folate metabolism. The popular combination drug trimethoprim-sulfamethoxazole inhibits folate metabolism at two points. Sulfonamides are inexpensive and they have a broad spectrum. Sulfonamides are usually used for gram negative infections such as urinary tract infections; however, they cover many gram positives, such as Staph aureus well. This is an ideal combination of effective broad coverage and low cost, except that sulfonamides have a slightly higher risk of severe drug reactions such as Stevens-Johnson syndrome. Additionally, sulfonamides result in acute hemolytic reactions in some patients with G6PD deficiency. Since we usually don't know who has G6PD deficiency and Stevens-Johnson syndrome can result in death or severe morbidity, these factors have tempered the popularity of sulfonamides. Law suits involving sulfonamides suggest that malpractice occurs when the clinicians fails to warn the patient of adverse reactions such as hemolytic reactions and Stevens-Johnson syndrome. Thus, if you intend to prescribe a sulfonamide to a patient, you must inform them of these risks (blood reaction if they have a hidden blood problem, or a severe allergic reaction which can result in death). In most instances after being informed of such risks, patients will prefer alternative antibiotics which have similar coverage and less side effects. In most instances, other antibiotics can provide the same coverage with less risk and similar cost. However, in patients with allergies to other antibiotics, sulfonamides may be useful. Additionally, if the patient's medical history indicates that they have used a sulfonamide in the past without problems, then their risk of an adverse reaction is substantially lower.

Quinolones

This class of antibiotics are related structurally to nalidixic acid. These drugs inhibit bacterial DNA synthesis by inhibiting B-subunit of DNA gyrase, an essential enzyme that allows DNA supercoils to be relaxed and reformed. Quinolones such as ciprofloxacin, norfloxacin and levofloxacin are very broad spectrum with coverage against Staph aureus (including MRSA), pneumococcus, Haemophilus influenzae, Mycoplasma, Chlamydia, gram negative enterics, Pseudomonas, etc.. Their main indication is in resistant urinary tract infections, but their broad spectrum makes them effective in other conditions. Their use is limited in pediatrics since they are currently contraindicated in children and pregnant women, because these drugs have impaired bone growth in laboratory animals.

Carbapenems

This new class of antibiotics target bacterial cell wall synthesis by inhibiting the transpeptidase enzymes required for peptidoglycan cross-linking. These drugs are very broad spectrum similar to high generation cephalosporins. Examples include imipenem and meropenem. These drugs have not been used commonly in pediatrics since they are most commonly used in highly resistant adult infections.

Macrolides and others.

The typical macrolide is erythromycin. These drugs inhibit bacterial ribosomal function. These drugs cover most streptococci and some Staph aureus. They also cover many atypical organisms such as Mycoplasma, Chlamydia, Legionella, Bordetella, Yersinia, Campylobacter, and Tularemia. Erythromycin ethylsuccinate (EES) and erythromycin estolate (also known as erythromycin propyl-laurel sulfate, or Ilosone) are commonly used. EES has less hepatic toxicity. Erythromycin estolate gets higher tissue levels and is commonly recommended for pertussis. Newer and more expensive erythromycins such as azithromycin and clarithromycin have broader coverage, less side effects and more convenient dosing. Azithromycin is dosed once a day for 5 days to give 10 days of clinical efficacy.

The tetracycline family (tetracycline, doxycycline, minocycline, etc.) shares some properties with erythromycins in that they inhibit bacterial ribosomal function and cover many of the same atypical organisms. Tetracyclines tend to be photosensitizers which limits their use in Hawaii. Tetracycline use is discouraged in children because it causes staining of teeth, hypoplasia of dental enamel, and abnormal bone growth in children.

Vancomycin is a glycopeptide which inhibits bacterial cell wall synthesis. It is available for IV since it is not absorbed from the GI tract. Vancomycin is broad spectrum and its major pediatric application is to cover resistant Staph aureus (MRSA) and resistant pneumococci. Vancomycin use is associated with a "red man syndrome" which is a histamine like reaction that can be inhibited by pretreatment with diphenhydramine and slowing the IV administration rate of the vancomycin. Vancomycin can also be given orally for pseudomembranous colitis caused by Clostridium difficile.

Clindamycin inhibits bacterial ribosomal function. It covers most streptococci and Staph aureus. Clindamycin covers most MRSA, but not 100%. If 100% coverage for Staph aureus is needed, then vancomycin is indicated. Clindamycin is a useful for the outpatient treatment of cellulitis and other infections commonly caused by group A strep and Staph aureus. Staph aureus resistance to clindamycin is present, but it is uncommon. Many clinicians treat cellulitis and other suspected outpatient Staph aureus conditions with clindamycin instead of cephalosporins since resistance to cephalosporins is too frequent. Clindamycin is also used for coverage of anaerobes including Bacteroides fragilis.

Chloramphenicol inhibits bacterial ribosomal function. Chloramphenicol is used infrequently because it has the potential to cause irreversible bone marrow suppression. It more commonly causes reversible bone marrow suppression which is not nearly as severe. Chloramphenicol covers all anaerobes similar to Clindamycin. Chloramphenicol crosses the blood brain barrier well and penetrates into the CSF, so it was frequently used to treat meningitis. Chloramphenicol has the unusual property of attaining high serum levels from oral administration. Most other drugs require IV administration to get high serum levels. When I was a resident in the early 80's, all children with bacterial meningitis would be treated initially with ampicillin and chloramphenicol. If the organism was resistant to ampicillin, then chloramphenicol would be used. These children could actually be switched over to oral chloramphenicol if starting an IV was difficult. CBCs would be checked daily or every other day to check for bone marrow suppression. Cephalosporins and vancomycin have largely replaced these older drugs to treat meningitis.

Metronidazole (Flagyl) is a anti-parasitic anti-amebic drug, but it also has nearly complete coverage of anaerobes. Thus, when 100% anaerobe coverage is required, the options include metronidazole, clindamycin or chloramphenicol. The broad spectrum penicillins in combination with clavulanate or sulbactam may also cover anaerobes sufficiently.

Questions

1. How many generations of cephalosporins are there?
2. Can the generation of the cephalosporin (in itself) be the sole selection criteria for a particular clinical situation?
3. List some organisms which cause the following entities: osteomyelitis, bacterial meningitis.
4. What empiric antibiotic(s) could be used to cover the organisms in the above question?
5. Select an empiric antibiotic for a 10 year old female who has a small pneumonia on chest x-ray. She is afebrile and has a frequent non-productive cough.
6. Select an empiric antibiotic for an 18 month old female with fever and pyuria on UA (i.e., suspected UTI)?
7. You decide to prescribe an erythromycin to a patient. You could prescribe erythromycin ethylsuccinate (EES) which is $10 for 40 tabs (1 tab q.i.d. for 10 days), or you could prescribe azithromycin (Zithromax) which is $70 for 6 tabs (two tabs today, then one tab daily for 4 more days). What considerations should be made in making such a decision?

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Answers to questions

1 and 2. There are at least four, and probably five, and possibly six. No doubt in the future, there will be more. How do these cephalosporins differ from each other and what characteristic places them in a given generation? The answer to this question is not an easy one. If you enter "fourth generation cephalosporin" into Medline's search engine, you will find some articles on fourth generation cephalosporins. Similarly, searches for fifth and sixth generation cephalosporin yields some articles. If I was a slick marketer of drugs, I would simply call my new cephalosporin "Tenth Generation" and almost everyone would buy it. However, what specific characteristic of the cephalosporin makes it clinically useful over other cephalosporins? If the drug was a tenth generation cephalosporin, but it had no clinical advantage over an existing third generation cephalosporin, then there is no need for a such a tenth generation cephalosporin. The generation is not nearly as important as the specific property of the cephalosporin which makes it clinically useful over another cephalosporin.

3. Osteomyelitis: Most likely Staph aureus. Bacterial meningitis: Pneumococcus, meningococcus, Haemophilus influenzae type B (HiB).

4. For osteomyelitis, we could cover the Staph aureus with an anti-Staph aureus penicillin such as oxacillin, nafcillin or methicillin or a first generation cephalosporin such as cefazolin. However, resistance to these drugs is currently about 25% to 30%. Although there is a good chance the patient will respond, in 25% to 30% of cases, this treatment will fail and the patient will suffer the consequences of inadequate treatment which would include: death from sepsis, Staph pneumonia, spread of the osteomyelitis, chronic osteomyelitis requiring an amputation, etc. None of these complications are minor, therefore, 75% coverage is inadequate. We need 100% coverage empirically since osteomyelitis is a serious infection. Thus, IV vancomycin is the treatment of choice here. For the bacterial meningitis case, we need an antibiotic to effectively cover these organisms and additionally, we need an antibiotic that will penetrate the blood brain barrier into the CSF. Chloramphenicol would be satisfactory here, but we don't use this because of its side effects. IV ceftriaxone or cefotaxime would penetrate the CSF well and cover meningococcus and HiB, and most pneumococcus, but pneumococcus has a small frequency of high level resistance to cephalosporins, so vancomycin must be added.

5. What organism is most likely? Mycoplasma or viral. Pneumococcus is unlikely since she is afebrile. The best antibiotic choice would be an erythromycin.

6. Although trimethoprim/sulfamethoxazole (Bactrim or Septra) is commonly recommended because of its broad coverage for this indication, this drug causes Stevens-Johnson syndrome more commonly than others. If the parents accept this increased risk, then this

should be documented on the chart. Most parents are not willing to accept this increased risk since other antibiotics are available. Amoxicillin will probably work, but there is a high frequency of resistance which is generally not a probably for simple cystitis, but in a febrile 18 month old, there may be some degree of pyelonephritis as well. Resistance to cephalosporins is infrequent. Thus, an acceptable answer here would also be a first generation cephalosporin such as cephalexin. IM ceftriaxone can also be given at the initial patient encounter to ensure high initial antibiotic levels and initial compliance.

7. Cost, compliance, convenience, efficacy, etc. While EES is $10 and azithromycin is $70, some patients may choose to pay more if the more expensive drug has significant advantages. Additionally, since most patients have drug plans, the difference may be negligible (e.g., $5 vs. $10). Compliance is essential for the drug to be effective. EES must be taken four times a day for 10 days while azithromycin is once a day for five days. Additionally, EES may have more GI side effects. Clearly a once a day medication is more convenient than a q.i.d. medication. If both medications are efficacious, perhaps it is best to discuss these differences with the patient and give them some input in the decision.

Chapter VI.6. Otitis Media and Otitis Externa

Vince K. Yamashiroya, MD

A parent brings her two year old son to your office because of a chief complaint of fussiness and tugging at his right ear for the past two days. He has had coughing and runny nose for about 5 days that has been treated with an over-the-counter cold medicine. He also has a low-grade fever of about 101 degrees axillary for the past two days. Both parents smoke cigarettes. He attends daycare. His past medical history is significant for ear infections in the past, with his last otitis media being 5 months ago treated with amoxicillin. His immunizations are up to date, including heptavalent pneumococcal vaccine.

Exam: VS T 38.4, P 100, RR 28, BP 100/65. He is active, alert to his surroundings and otherwise in no distress. HEENT: Right tympanic membrane is erythematous and bulging with poor mobility on pneumatic otoscopy. Left TM is clear with good mobility. Throat is non-erythematous. There are shotty cervical lymph nodes. Lungs are clear to auscultation. The rest of the examination is normal.

He is diagnosed with acute right otitis media. He is prescribed amoxicillin and acetaminophen. A follow-up visit is scheduled in 10 days.

Otitis media (OM) is one of the most common diagnoses that pediatricians encounter. It is estimated that otitis media comprises 23% of all office visits in the first year of life, and 40% at four to five years when these children start Kindergarten. In the United States, OM was the most frequent diagnosis in office settings, and accounted for 24.5 million visits in 1990 according to a report published by the Centers for Disease Control and Prevention (CDC) (1).

The middle ear is a gas filled cavity in the petrous part of the temporal bone between the external auditory canal and the inner ear. It contains three ossicles called the malleus, incus, and stapes. These ossicles conduct sound from the external auditory meatus to the inner ear. Therefore, factors hindering the movement of these ossicles, such as pus or fluid in the middle ear, will adversely affect hearing. The middle ear is connected to the nasopharynx by the eustachian tube. The eustachian tube allows for ventilation and clearance of fluid from the middle ear. Compared to the adult, the infant's eustachian tube is shorter, has a more acute angle, and has a smaller luminal area. Also, the angle of the tensor veli palatini muscle to the cartilage around the tube is variable, compared to being stable in the adult. The significance of these characteristics is that there is a greater likelihood that nasopharyngeal secretions can reflux or insufflate into the middle ear, and that clearance of the middle ear cavity of these secretions is decreased (2). These differences are the reason why there are more middle ear infections in the infant compared to the adult and older child.

Otitis media is common in infants and young children with the peak age being between 6 to 18 months of age. This is due not only to anatomical factors, but immunologic as well since these children still lack many protective antibodies against viral and bacterial organisms. The incidence of OM decreases after the first year of life and then increases again when the child enters school. It becomes less common after 7 years of age. Factors that increase the risk for OM are attendance in day care, second hand cigarette smoke exposure, craniofacial abnormalities such as cleft palate, and immunologic deficiencies. A protective factor is breastfeeding, which may be due to immune factors (e.g., secretory IgA and IgG), non-immune factors (e.g., interferon, glycoproteins, lactadherin), and anti-inflammatory factors (e.g., antioxidants, TNF-alpha, lactoferrin). Also, babies are breast fed while in a vertical or semi-reclining position, compared to some babies who may be bottle-fed while in a horizontal position. The practice of bottle feeding in the supine position is thought to increase OM by reflux of fluids from the nasopharynx into the middle ear (1).

The diagnosis of otitis media is a challenging one for pediatricians because of difficulty obtaining an adequate examination of the tympanic membrane (TM). The presence of cerumen and uncooperative and frightened patients complicate this. Common symptoms of OM are otalgia, otorrhea, and hearing loss. However, infants may only manifest otalgia by fussiness in the presence of fever. Other less common symptoms of OM and its complications are vertigo, nystagmus (unidirectional, horizontal, jerk type), tinnitus, swelling in the posterior auricular area (associated with mastoiditis), facial paralysis (due to disease within the temporal bone), and purulent conjunctivitis (which is associated with non-typable Haemophilus influenzae) (3). The best tool for the diagnosis of OM is the pneumatic otoscope. Inspection of the TM should include four characteristics: position, color, degree of translucency, and mobility. Also by visualizing the TM, one notices several landmarks such as the malleus which is divided into the short process, manubrium, and umbo; the long process of the incus; and the pars flaccida on the superior aspect and the pars tensa on the inferior aspect (3). It should be noted, although controversial, that a tympanic membrane may become red in a crying child (4). Other methods of diagnosing OM include tympanometry and tympanocentesis (3). This chapter will focus on two types of otitis media, namely acute otitis media and otitis media with effusion.

Acute otitis media (AOM) typically presents as a sudden onset of otalgia, fever, and hearing loss, which are preceded by an upper respiratory tract infection lasting for several days. Fever occurs in about 30-50% of patients of AOM, and is usually less than 40°C. Fever over 40°C suggests bacteremia or another complication (4). Pneumatic otoscopy reveals the TM that is opaque and bulging with poor mobility. Erythema, is a characteristic finding, but it may be absent. There may be perforation. Otitis media with effusion (OME), on the other hand, is asymptomatic in most children. Some may complain of hearing loss and less commonly tinnitus and vertigo. Older children may complain of a "plugged" feeling or "popping" in their ears, which is usually bilateral. The TM commonly appears opaque, but may be

retracted or full. An air fluid level or bubbles may be seen. Mobility is also decreased. It is important to distinguish between the two diseases because the management of each is different, however, it is not easily done. Some key points would be that fever, irritability, definite redness and otalgia, and a bulging and opaque eardrum are associated with AOM, whereas absence of symptoms except for hearing loss, and a retracted eardrum are associated with OME. Both can present with middle ear effusion and decreased mobility of the TM (6,7).

If severe otalgia is present, then analgesia becomes a major therapeutic consideration. Minor pain can be treated with acetaminophen or ibuprofen in most instances. For more severe pain, topical anesthesia with benzocaine containing ear drops (e.g., Auralgan otic) can be administered in the office to see if satisfactory analgesia is achieved. If not, a stronger analgesic such as acetaminophen with codeine may be necessary. Although Auralgan otic is used for pain relief, one should be aware of allergic reactions and to make sure there is no perforation.

The management of otitis media is one of many controversial subjects in pediatrics. Most treat AOM with antibiotics as soon as it is diagnosed, whereas in OME, antibiotics may be deferred, unless it becomes chronic (3). The three most common organisms are Streptococcus pneumoniae, non-typable Haemophilus influenzae, and Moraxella catarrhalis. Other less common organisms are Streptococcus pyogenes, Staphylococcus aureus, gram negative enteric bacteria, and anaerobes (5). The choice of antibiotic is dependent on efficacy, palatability, side effects, convenience of dosing, and cost. The drug of choice against AOM remains amoxicillin, although bacterial resistance continues to be a problem. For this reason, it is recommended that the dose of amoxicillin be increased from 40-50 mg/kg/day to 80-90 mg/kg/day in two to three divided doses. However, children who are at low risk for resistant organisms may be treated with the lower dose of amoxicillin, being 40-50 mg/kg/day. Risk factors include young age (less than 2 years), recent antibiotic use (within the last month), and day care attendance (4). The consensus is less clear on second-line therapy if amoxicillin fails. The CDC suggests three drugs, amoxicillin-clavulanate (with the amoxicillin component of 80-90 mg/kg/day), cefuroxime axetil, and intramuscular ceftriaxone. In patients who are allergic to beta-lactam antibiotics, macrolides, like erythromycin plus sulfisoxazole, azithromycin, or clarithromycin, and trimethoprim-sulfamethoxazole may be used. The duration for treatment is 10 days, although azithromycin, cefpodoxime, and cefdinir are now approved for 5 days, and a single dose of intramuscular ceftriaxone is as effective as a 10-day course of amoxicillin. Also recently, azithromycin has been approved for a 30 mg/kg one time dose, or 10 mg/kg dose for three days. If the 30 mg/kg dose is used however, there is a 4.9% risk for emesis occurring, necessitating a repeat dose of medication. Other drugs that are recommended are cefprozil, ceftibuten, loracarbef, and clindamycin (6). The expected clinical course is improvement within 48-72 hours. Persistent otalgia, fever, and other systemic symptoms past 72 hours should be reevaluated. At times, tympanocentesis or myringotomy is necessary for resistant cases, at which time a culture can also be obtained. Follow-up visits are recommended 10-14 days later to determine the need for further antimicrobial treatment. Although a middle ear effusion may be present, an inflamed eardrum or persistent systemic symptoms at this follow-up visit may warrant changing the antibiotic therapy or performing a myringotomy/tympanocentesis. It is estimated that 30-70% of children will have a middle ear effusion 10-14 days later, and that without treatment, 6-26% will have a persistent middle ear effusion after 3 months, with the mean of resolution being about 23 days. Because middle ear effusions usually resolve spontaneously, the CDC and the American Academy of Pediatrics have recommended against re-treatment of infants and children who have persistent middle ear effusions and are asymptomatic. However, there is debate about what to do for children having OME for 2-3 months. An option is to treat non-surgically. Medications that have been studied are decongestants, antihistamines, oral corticosteroids, and antibiotics. The only drugs proved efficacious are oral corticosteroids and antibiotics; however, it is felt that the side effects from oral corticosteroids outweigh its benefits. Therefore, a ten-day course of amoxicillin remains as a reasonable treatment for chronic OME. Other antibiotics that have been recommended are cefaclor, erythromycin-sulfisoxazole, and ceftibuten, although these are either just as efficacious or less so than amoxicillin. Some of the decisions to treat chronic OME are significant conductive hearing loss; young infant since they cannot communicate their symptoms; associated suppurative upper respiratory tract infection; concurrent permanent conductive and sensorineural hearing loss; speech-language delay because of effusion and hearing loss; alterations in the tympanic membrane such as a retraction pocket; middle ear changes such as adhesive otitis media or involvement with the ossicles; previous surgery for otitis media; frequent recurrent episodes; and persistence of the effusion for 3 months or longer in both ears or 6 months or longer in one ear. If antibiotic therapy fails, then myringotomy with tympanostomy tube placement or myringotomy and adenoidectomy are recommended as the next step. Only ofloxacin otic solution is approved in children with acute otitis media with tympanostomy tubes or chronic suppurative otitis media with perforation (8).

Not only do we treat otitis media for symptomatic relief, but also to prevent its complications. The complications of OM include conductive and sensorineural hearing loss, mastoiditis, cholesteatoma, labyrinthitis, facial paralysis, meningitis, brain abscess, and lateral sinus thrombosis (9,10). Fortunately, because we live in the antibiotic era, these complications are rarely seen.

The prognosis for otitis media is excellent. In most children, otitis media resolves after antibiotic therapy. Only in a few children does medical therapy fail, and more aggressive measures are needed, such as myringotomy and tympanostomy tubes. Recently, a heptavalent pneumococcal conjugate vaccine (Prevnar) has been FDA approved and is a recommended childhood immunization by the AAP and CDC. This vaccine has been shown to reduce otitis media caused by pneumococcus; however, its greatest efficacy is in those patients with recurrent OM.

Otitis externa is another condition that is often seen in pediatrics. Four factors can lead to the development of otitis externa. They are excessive wetness (e.g., swimming), dryness (e.g., lack of cerumen and dry ear skin), other skin diseases (e.g., dermatitis, previous infection), and trauma (e.g., using cotton tipped applicators). It is also called swimmer's ear, although it can occur without swimming (4). The pathophysiology of otitis externa is the following. As the humidity in the outer ear increases, the stratum corneum in the cartilaginous portion of the ear absorbs water, which results in edema. Edema blocks the pilosebaceous units in the ear, thereby decreasing the excretion of cerumen. A decrease in cerumen causes an increase in the pH of the external ear, in addition to decreasing its water repelling covering. The exposed skin becomes susceptible to maceration and the higher pH becomes a favorable environment for bacteria such as Pseudomonas. Bacteria can then penetrate through the dermis after superficial breakdown or through minor trauma such as with cotton applicators. Inflammation and infection thus results. The most common organisms cultured in otitis externa are Pseudomonas and Staphylococcus aureus. Other organisms that can be cultured are Enterobacter aerogenes, Proteus mirabilis, Klebsiella pneumoniae, streptococci, coagulase-negative staphylococci, diphtheroids, and fungi such as Aspergillus and Candida. Symptoms initially include pruritus and aural fullness, which then progresses to ear pain that may be severe and out of proportion to its appearance. Purulent otorrhea and hearing loss from edema of the canal may be present as well. Examination shows an inflamed and erythematous cartilaginous canal, with variable involvement of the bony canal. Manipulation of the pinna and pressure on the tragus elicits pain. Although the tympanic membrane is not affected, it and the medial portion of the canal can become involved and often look granular. When this happens, pneumatic otoscopy is needed to rule out concomitant otitis media. Tender and palpable lymph nodes may be present in the periauricular

and preauricular areas. Treatment includes the use of ototopical drops, such as a combination of polymyxin B, neomycin, and hydrocortisone (Cortisporin otic). Polymyxin B is active against gram negative bacilli such as Pseudomonas, neomycin is active against gram positive organisms and some gram negatives especially Proteus, and the corticosteroid reduces inflammation and edema. Fluoroquinolones are a new class of antibiotics for otitis externa; ofloxacin and ciprofloxacin are both currently available. If there is a lot of fluid drainage, it may be preferable to wick out most of the fluid prior to instilling the drops. If there is severe edema preventing effective instillation of drops, a wick can be placed in the membranous canal with otic drops applied several times a day, the wick can be replaced every 48 to 72 hours until the edema resolves (11). After 2-3 days, the edema of the ear canal is usually markedly improved. Analgesics such as ibuprofen and codeine can be used to treat severe pain. Cleaning the ear canal such as irrigating with 2% acetic acid to remove debris can be a useful adjunct to therapy. Prevention may be necessary for those patients who suffer from recurrences. Dilute alcohol or acetic acid (2%) can be instilled immediately after swimming or bathing, and is the best prophylaxis. Patients should protect their ears from water when bathing and should avoid swimming until their otitis externa resolves (4).

Questions

1. When is the peak age of otitis media?
2. What are some risk factors for otitis media?
3. What is the BEST tool for diagnosing otitis media (not gold standard)?
4. What is the difference between acute otitis media and otitis media with effusion?
5. What are the three most common organisms that cause otitis media?
6. What antibiotic is the drug of choice against otitis media?
7. What are the three second-line antibiotics recommended by the CDC if amoxicillin fails?
8. What are some reasons to treat chronic otitis media with effusion with either antibiotics or tympanostomy tubes?
9. What are some complications of otitis media?
10. What is the most common organism cultured in otitis externa?
11. What are four factors that can predispose a patient to develop otitis externa?
12. What can be instilled in the ear to prevent otitis externa in an otitis externa prone child?

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Answers to questions

1. 6 to 18 months of age.
2. Attendance in day-care, second-hand cigarette smoke exposure, craniofacial abnormalities, bottle-feeding in the horizontal position.
3. Pneumatic otoscopy (myringotomy/tympanocentesis is the gold standard, but not the best diagnostic tool because of its invasiveness).
4. AOM: otalgia, fever, hearing loss, associated with upper respiratory tract infection; TM that is opaque or erythematous and bulging with poor mobility, perforation. OME: commonly asymptomatic but may have hearing loss; retracted TM.
5. Streptococcus pneumoniae, non-typable Haemophilus influenzae, Moraxella catarrhalis.
6. Amoxicillin
7. Amoxicillin-clavulanic acid, cefuroxime axetil, intramuscular ceftriaxone
8. Significant conductive hearing loss; young infant since they cannot communicate their symptoms; associated suppurative upper respiratory tract infection; concurrent permanent conductive and sensorineural hearing loss; speech-language delay because of effusion and hearing loss; alterations in the tympanic membrane such as a retraction pocket; middle ear changes such as adhesive otitis media or involvement with the ossicles; previous surgery for otitis media; frequent recurrent episodes; and persistence of the effusion for 3 months or longer in both ears or 6 months or longer in one ear.
9. Conductive and sensorineural hearing loss, mastoiditis, cholesteatoma, labyrinthitis, facial paralysis, meningitis, brain abscess, and lateral sinus thrombosis.
10. Pseudomonas aeruginosa.
11. Excessive wetness, lack of cerumen, preexisting skin problems, and trauma.
12. 2% acetic acid or dilute alcohol.

Chapter VI.7. Sinusitis
Kathleen A. Morimoto, MD

A 7 year old previously healthy female presents to her primary care physician with a 12 day history of persistent thick nasal discharge, nasal congestion, cough, and intermittent low grade fever. On further questioning, her parents reveal that the cough is worse at night but there is no wheezing, currently or in the past. She also seems to have one temperature spike daily to about 38.2 degrees (100.8 degrees F). She is not taking any medications. They deny the possibility of a nasal foreign body. She denies any vomiting, headache, earache, or rashes.

Her past medical history is negative for hospitalizations, asthma, allergic rhinitis, or cystic fibrosis.

Exam: VS T 37.2, P 90, R 15, BP 88/50. She is an alert, interactive female breathing comfortably. She has no eye abnormalities. Her tympanic membranes are clear. She has nasal congestion with thick yellow purulent mucus in the posterior nasal pharynx. Her nasal turbinates are red and swollen. Transillumination of her sinuses is equivocal. She has mild tenderness to palpation of her maxillary sinuses. Her oral pharynx is non erythematous. Her breath is malodorous. She has no obvious dental caries or pain on tapping of her teeth. Her lungs are clear. The rest of her exam is normal.

A diagnosis of acute bacterial sinusitis is made on the basis of history and physical exam. She is started on amoxicillin at 50mg/kg/day for 10 days. Her symptoms quickly resolve, and by day 3 of treatment she is asymptomatic.

Sinusitis is a common childhood disease which involves inflammation of the paranasal sinuses (frontal, maxillary, ethmoid, and/or sphenoid). There are many etiologies and forms of sinusitis, including the simple self limited viral rhinosinusitis, the acute bacterial, subacute, and chronic sinusitis. The differences between these designations lie largely in the duration of symptoms.

In acute bacterial sinusitis, nasal and sinus symptoms have been present for at least 10 days, but fewer than 30 days. Subacute sinusitis involves nasal and sinus symptoms lasting longer than 4 weeks but fewer than 12 weeks, and chronic sinusitis involve symptoms lasting at least 12 weeks (1).

Anatomically, the maxillary and ethmoid sinuses form during the third and fourth gestational month, but at birth are still very small. The frontal sinuses develops by one to two years of age and assume their final position above the orbital ridge by the fifth or sixth birthday. However, the frontal sinuses are not completely developed until late adolescence. The frontal, ethmoid, and maxillary sinuses all drain through the ostiomeatal complex located between the middle and inferior turbinates. This makes normal mucociliary motility imperative to preventing sinus infections. In the absence of effective clearing of secretions by the cilia, the sinuses become a medium for bacterial growth. Thus, anything that impairs normal ciliary function such as cigarette smoke exposure, viral infections, allergic rhinitis, cystic fibrosis, immunodeficiency, gastroesophageal reflux, and ciliary dyskinesia, can predispose patients to developing sinusitis. Nasal obstructions caused by foreign bodies, polyps, large adenoids, cleft palate, and trauma are also risk factors for sinusitis. However, viral infections represent the inciting event in about 80% of cases of acute sinusitis with allergic inflammation accounting for about 20% of acute sinusitis. It is estimated that the typical child has 6-8 viral URIs per year and approximately 10% of these may be complicated by secondary bacterial sinusitis.

The principle bacterial pathogens implicated in bacterial sinusitis are Streptococcus pneumonia (30%), non-typable Haemophilus influenzae (20%), and Moraxella catarrhalis (20%) (2). Viral isolates include adenovirus, parainfluenza virus, influenza, and rhinovirus, which account for 10% of sinusitis cases. In chronic sinusitis, results have been variable with alpha hemolytic streptococci, Staphylococcus aureus, anaerobes, and mixed colonies frequently recovered.

The most common presenting patient complaint is persistent nasal discharge which can be of any quality from thin, thick, clear, or purulent. Other common complaints include persistent cough which is worse at night, malodorous breath, low grade fever, dental pain, and sore throat. Older children, teens, and adults will have more specific complaints such as facial pain and pressure, and headaches.

On physical exam it is often difficult to differentiate between uncomplicated viral rhinosinusitis and acute bacterial sinusitis. Both conditions will have mild erythema and swelling of the nasal turbinates with mucopurulent nasal discharge. Sinus tenderness can be useful in the older child and adolescent, but is unreliable in younger children. Transillumination of the sinuses may be useful to assess the presence of fluid in the maxillary and frontal sinuses. However, this technique is difficult to perform correctly and has been shown to be unreliable in children less than 10 years old due to asymmetrical sinus development or lack of sinus development.

Sinus aspiration remains the gold standard for the diagnosis of acute bacterial sinusitis. However, it is invasive and requires a skilled ENT surgeon. Subsequently less invasive tests such as sinus x-rays, sinus CT scans, and MRI's have been used to help confirm the diagnosis of sinusitis. Radiographic findings of sinusitis are complete opacification, mucosal thickening of at least 4mm, or an air fluid level. However, even in the presence of these x-ray findings it will not help differentiate between viral rhinosinusitis, acute or chronic sinusitis.

In September 2001, the American Academy of Pediatrics published a clinical practice guideline for the management of sinusitis. Part of their recommendations include appropriate diagnosis and use of imaging studies to confirm sinusitis. In short, they recommend that for children <6 years of age, the diagnosis of acute bacterial sinusitis be based on clinical criteria rather than radiographic criteria. In this age group, there was an 88% correlation between history (persistent cough and nasal symptoms) and abnormal sinus radiographs, thus reducing the benefit of x-rays. Furthermore, the guidelines recommend reserving sinus CT scans for those patients requiring evaluation for surgery (2).

The treatment for acute bacterial sinusitis is antibiotics. In uncomplicated sinusitis the treatment is standard dose amoxicillin of 45-50 mg/kg/day. However, alternate dosing or medication should be considered if a patient fails to improve on conventional doses of amoxicillin, recent treatment with amoxicillin (<1 month ago) or attendance at day care. Alternate drug regimens recommended in these cases are high dose amoxicillin of 80-90 mg/kg/day and amoxicillin with clavulanate (1,2). Appropriately treated sinusitis patients will have a marked improvement in nasal discharge and cough within 48-72 hours.

The duration of antibiotic therapy has been controversial, between 10-28 days. Recent recommendations suggest continuing antibiotics until the patient is symptom free, plus an additional 7 days, but for a minimum of 10 days.

Surgical treatment is seldom indicated in acute sinusitis. However, in cases where patients fail to respond to aggressive antimicrobial therapy, or suffer from refractory chronic sinusitis, sinus aspiration may be indicated. Sinus aspiration is useful to both ventilate the sinuses and obtain cultures. Surgical intervention for chronic sinusitis involves endoscopic enlargement of the ostiomeatal complex and anterior ethmoidectomy. However, the actual outcome and benefit of sinus surgery is not well established.

The vast majority of acute bacterial sinusitis resolves without problems. The few reported complications associated with sinusitis involve contiguous spread of infection to the orbit, bone, or central nervous system. Orbital involvement is the most likely, and can lead to periorbital and orbital cellulitis, orbital abscess, and subperiosteal abscess. Other documented complications include frontal osteomyelitis (Pott's puffy tumor), epidural abscess, subdural empyema, cavernous sinus thrombosis, and meningitis.

Questions

1. What is the dose and drug of choice for uncomplicated sinusitis?
2. What percentage of viral URI's will progress to acute bacterial sinusitis?
3. Name some risk factors in the development of sinusitis.
4. What are some radiographic finding of sinusitis?
5. What is the most common complication of sinusitis?

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Answers to questions

1. Amoxicillin 45-50 mg/kg/day.
2. Up to 10% will progress.
3. Allergic rhinitis, viral infections, cystic fibrosis, foreign body.
4. Mucosal thickening of at least 4mm, air fluid levels, opacification.
5. Periorbital cellulitis.

Chapter VI.8. Mastoiditis

Kathleen A. Morimoto, MD

A 7 year old male presents to the ER with a two day history of worsening ear pain and drainage. On the day prior to presentation, his parents noted redness behind his right ear, and that his right ear appeared to be sticking out. He had been well until 10 days ago when he started complaining of a cough and runny nose that progressed to include right ear pain and fever. He was evaluated in the clinic 5 days ago and diagnosed with an acute right otitis media. He was placed on amoxicillin and he initially appeared to improve until two days ago when his ear pain recurred and this is now accompanied by ear drainage, redness behind his right ear, and a prominent right pinna which is pointing up and out.

Exam: VS T 38.5, P 110, R 20, BP 100/60. He is non toxic, alert and responsive. His head is normocephalic. His eyes are normal. His left TM and ear are normal. His right pinna is upward and outwardly displaced with erythema and tenderness to the right mastoid. There is purulent drainage from his right ear which is obstructing visualization of tympanic membrane. His throat and neck are normal. Heart regular without murmurs. Lungs are clear. He has good strength (5/5) in all four extremities. His DTRs are 2+ in all four extremities. He ambulates well without ataxia

A CT scan of the mastoids is performed which demonstrates haziness and early bony destruction of the mastoid. No coalescence of air cells, empyema or subperiosteal abscess is noted. The patient is hospitalized for parenteral antibiotics. An ENT consult is obtained. The patient defervesces by 48 hours and he is then taken to the OR for myringotomy and tympanostomy tube placement. Long term IV access is placed and he receives 4 weeks of parenteral antibiotics. Following completion of therapy the patient does well without sequelae.

Mastoiditis is a suppurative infection of the mastoid air cells, and a potential complication of otitis media. Mastoiditis can basically be broken down into two types, acute and chronic. The acute form is defined as symptoms lasting less than one month and chronic for symptoms greater than one month. Within acute mastoiditis there are two pathologic forms, acute mastoiditis with periostitis, and acute mastoiditis with osteitis (with or without subperiosteal abscess). This section will be focusing on acute mastoiditis, as chronic mastoiditis is a unique entity in itself.

Prior to the antibiotic era, mastoiditis was a common complication of acute otitis media and frequently resulted in death. In 1938, the frequency of mastoidectomy for acute mastoiditis was 20%. With the advent of antibiotics, the frequency of mastoidectomy for acute mastoiditis had declined to 2.8% by 1948 with an almost 90% reduction in mortality rate (5).

The mastoid process is the posterior part of the temporal bone. At birth, the mastoid consists of a single cell called the antrum, which is connected to the middle ear by a narrow channel called the aditus ad antrum. Soon after birth, the mastoid undergoes pneumatization and by 2 years of age, is well pneumatized. Anatomically, the mastoid is surrounded by numerous vital structures, so if it become infected, this can lead to devastating results. Anterior to the mastoid lies the middle ear and ossicles, the facial nerve, the jugular vein, and the internal carotid artery. Posteriorly, lies the posterior cranial fossa and sigmoid sinus. Superior to the mastoid is the middle cranial fossa and medially the mastoid encases the cochlea and semicircular canals. Inferior to the mastoid are extensive soft tissue planes and muscles that are also potential areas for the spread of infection.

In acute otitis media, a certain amount of mastoid inflammation is observed because the mastoid air spaces and middle ear cavity are contiguous and they share the same modified respiratory epithelium. With appropriate antibiotic therapy, the inflammation within the middle ear and mastoid resolves. However, if the acute otitis media is not treated or inadequately treated, the inflammation within the mastoid persists. In acute mastoiditis, this persistence of inflammation results in accumulation of serous then suppurative material within

the mastoid. Accumulation of the purulent exudate leads to increased middle ear pressure resulting in possible tympanic membrane perforation. The increased pressure in the mastoid causes destruction of the bony septa between the air cells leading to formation of large cavities. Subsequently, osteomyelitis of adjacent bone may develop as well as abscess formation and bony erosion with extension of infection into surrounding structures.

The clinical manifestations of acute mastoiditis are largely dependent on the age of the patient and the stage of the disease. The classic presentation however, is a febrile child with otalgia, mastoid swelling and tenderness, and a history of acute otitis media days to weeks ago. The patient may have received antibiotics with some temporary improvement before becoming ill again. Other signs and symptoms of mastoiditis include mastoid erythema, displaced auricle either up and out in an older child or down and out in an infant, otorrhea, and a bulging immobile tympanic membrane.

The diagnosis of acute mastoiditis can be made on clinical findings alone. However, if radiographic imaging is indicated, CT scan is the test of choice over plain radiographs. CT scans done early in the course of mastoiditis reveal clouding of the mastoid, however this is not diagnostic as 50% of patients with uncomplicated acute otitis media will have similar findings. True CT evidence of mastoiditis is destruction of the mastoid outline, loss of bony septa within the air cells, "coalescence" of mastoid air cells (loss of bony septa between air cells), and hypoaeration of the mastoid (1,2). Additionally, CT scans with contrast are helpful in delineating possible intracranial complications.

Cultures of middle ear aspirates, ear drainage in the case of a perforated TM, and/or actual mastoid cultures may be helpful in optimal management of mastoiditis. If the TM is intact, cultures obtained from middle ear aspirates have been shown to correlate with actual mastoid cultures. However, if the TM is perforated, cultures obtained are often contaminated by ear canal flora. Consequently, in these cases, cultures should be obtained as close to the perforation site as possible. Optimally cultures should be obtained prior to the initiation of antibiotics. Unfortunately this is not always feasible particularly if the patient is not stable for surgery.

Although intuitively one would expect the same organisms that cause acute otitis media to also cause acute mastoiditis, the actual microbiology differs. The most common bacteria isolated in acute mastoiditis are Streptococcus pneumonia, Streptococcus pyogenes, and Staphylococcus aureus. Pseudomonas, enteric gram negative rods, and Staphylococcus aureus are the three most common organisms isolated in patients with chronic mastoiditis (2).

Initial antibiotic therapy in acute mastoiditis is empiric. Based on the most likely organisms, oxacillin and cefotaxime have been recommended (1). Vancomycin may be preferable since the frequency of oxacillin and cephalosporin resistant Staph aureus (MRSA) exceeds 25% in most areas. Additionally, emerging pneumococcal resistance may also benefit from vancomycin treatment. Ceftazidime or other anti-pseudomonas therapy may be indicated if pseudomonas is suspected. Duration of therapy is similar to that of osteomyelitis, and depends on the organism, extent of disease, and clinical response. However, a minimum of three weeks is recommended (1).

Surgical treatment of acute mastoiditis depends on the severity of the disease. In cases of simple uncomplicated mastoiditis (acute mastoiditis with periostitis), IV antibiotics and myringotomy and tympanostomy tube placement are recommended (5). If the patient fails to respond to the above therapy, or the mastoiditis is complicated by osteitis with or without subperiosteal abscess, the addition of a simple mastoidectomy is indicated (2,5). In a simple mastoidectomy, the mastoid air cell system is eviscerated although the canal walls are left intact. In severe cases refractory to simple mastoidectomy, a modified radical or radical mastoidectomy may be indicated. These surgical procedures involve complete removal of the mastoid air system including the posterior ear canal wall thereby creating a single cavity between the mastoid, middle ear, and external auditory canal. In addition, the radical mastoidectomy removes the tympanic membrane, malleus, and incus thereby leaving just the stapes or portion of the stapes intact.

The associated complications of acute mastoiditis are dependent on how and where the infection spreads. Pus that erodes through the lateral aspect of the mastoid produces a subperiosteal abscess. Clinically this child will present with redness, swelling, or pain behind the ear over the mastoid process. Pus can also spread medially to the petrous air cells resulting in petrositis or spread to the occipital bone posteriorly leading to osteomyelitis of the calvarium (Citelli abscess). Infection could also spread and involve the facial nerve, and central nervous system leading to meningitis, epidural and cerebellar abscesses, subdural empyema, or venous sinus thrombosis. The middle ear ossicles can also be destroyed resulting in conductive hearing loss. Rarely, mastoiditis is associated with abscess formation beneath the sternocleidomastoid and digastric muscles (Bezold abscess) (2,5).

The prognosis of mastoiditis depends on the extent of the infection. Fortunately, if detected early prior to intracranial involvement, the prognosis is very good. Even sensorineural and conductive hearing deficits associated with mastoiditis may be reversible if treated early. Therefore, prevention with early and adequate treatment for acute otitis media and early recognition of mastoiditis are key in decreasing the risk of serious suppurative complications.

Questions

1. What are the three most common organisms in acute otitis media?
2. What are the three most common organisms in acute mastoiditis?
3. Name a few intracranial complications of acute mastoiditis.
4. Name a few extracranial complications of acute mastoiditis.
5. Classically what is the difference in ear position in acute mastoiditis between the older child and young infant?
6. True/False: A CT scan image demonstrating clouding of the mastoid air cells is diagnostic of mastoiditis (acute or chronic)?
7. True/False: Plain film radiographs of the mastoid air cells often show mastoid clouding in acute otitis media without true mastoiditis.

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Answers to questions

1. S. pneumonia, H. influenzae (non-typable), and M. catarrhalis.
2. S. pneumonia, S. pyogenes, and S. aureus.
3. Meningitis, epidural empyema, subdural empyema, venous sinus thrombosis.
4. Facial nerve paralysis, deafness, labyrinthitis, petrositis, Bezold abscess.
5. In the older child the ear is up and out and in the infant it is down and out.
6. False
7. True

Chapter VI.9. Oral and Upper Respiratory Infections
Joel Ruff, MD

A 15 year old boy comes to the office for a sore throat. His sore throat started three days ago but it was mild. He was unconcerned and did not seek medical attention. He denies any initial fever, vomiting, diarrhea, rash, rhinorrhea or cough. Last night, his sore throat became worse, seeming to be more painful on the right. This morning it was so sore he could hardly swallow or open his mouth and the pain is still worse on the right. He has been well otherwise and cannot remember when he last had a sore throat. His energy level is normal and he denies other symptoms except for the severe pain.

Exam: VS T 39.0, P 100, R 20, BP 130/84. In general, he looks uncomfortable although not toxic. He has difficulty opening his mouth wider than 2 cm. His speech has a "hot potato" (muffled) quality to it. His mucous membranes are moist. An asymmetric erythematous swelling (greater on the right) and deviation of the uvula to the left are seen. The right side of his soft palate is also noted to be slightly bulging. His neck is supple with tender adenopathy on the right side. The remainder of his general physical examination is normal including lungs, heart, abdomen, extremities and skin.

He is referred to the emergency room. A diagnosis of peritonsillar abscess is made and he undergoes incision and drainage, spending a few days in the hospital for IV antibiotics and pain control. He is discharged in good condition a few days later.

Upper respiratory infections include infectious conditions of the nose, adenoids, tonsils, pharynx, oral cavity and larynx. The following terms are often used: Rhinitis (nose), tonsillitis (tonsils), pharyngitis (pharynx), nasopharyngitis (nose and pharynx), stomatitis (mouth), gingivitis (gums), gingivostomatitis (gums and mouth), uvulitis (uvula), glossitis (tongue), laryngitis (larynx), parotitis (parotid gland). Sinusitis and otitis media are discussed in separate chapters.

Pharyngitis is a ubiquitous condition that accounts for a large number of visits to the physician. Fortunately, the majority of causes of sore throat have a benign course requiring only symptomatic treatment. It is important, however, to have an understanding of some of the less common, but potentially more serious etiologies of pharyngitis and their sequelae.

The tonsils are the site of most of the infections discussed below. They, along with the adenoids superiorly and lingual tonsils inferiorly, form a ring of lymphatic tissue known as the Waldeyer ring. What is referred to most commonly as "tonsils" are the palatine tonsils, the lateral limits of the ring. The tonsils are bounded by the palatoglossus muscle or "anterior pillar" and palatopharyngeal muscle or "posterior pillar." The structures have multiple folds which increase surface area available for antigenic stimulation. When an antigen is presented, it stimulates B cells that have congregated there. Migration of more lymphocytes to the site occurs and there they differentiate into immunoglobulin producing cells. Although IgM and IgG are found, the majority of the secretion consists of IgA. A wide variety of organisms can cause infection in this area, including viruses, bacteria, fungi and parasites (1,2).

Viruses cause the majority of pharyngitis with rhinovirus being the most common, followed by coronavirus and adenovirus in one series (3). Upper respiratory infection etiologies are frequently age dependent. For example, respiratory syncytial virus (RSV) will cause cold symptoms in teens and adults, while it causes bronchiolitis in infants and pneumonia in small and/or premature infants. Parainfluenza virus causes colds in teens and adults, while it causes croup in young children.

A long list of other viruses may also cause infection including influenza, herpes simplex virus (HSV), coxsackie virus, Epstein-Barr virus (EBV), cytomegalovirus (CMV) and human immunodeficiency virus (HIV). While the majority of viral infections have nonspecific symptoms, a few virus types give clues to their identity in how they present.

Adenovirus, for example may cause an associated conjunctivitis, the combination of which is known as "pharyngoconjunctival fever" (3,4). Herpes and coxsackie virus may produce ulcerations on the oral mucosa (stomatitis). HSV type 1 tends to be the more common subtype of HSV, but oral-genital exposure to HSV type 2 may also produce similar lesions. The lesions from HSV tend to, but not exclusively be more anterior in the mouth and often involve the gums (known as gingivostomatitis) (3). Lesions from coxsackie virus, which is a subtype of enterovirus, may appear similarly as multiple vesicles on an erythematous base (commonly seen on the palate), and are known as herpangina. The lesions in the latter may be associated with vesicles on the hands and feet and in this case are known as "hand-foot-and-mouth disease." Both types of oral ulcerations are very painful.

Epstein-Barr virus infection, also known as infectious mononucleosis, is manifested classically as exudative pharyngitis, fever, lymphadenopathy, hepatosplenomegaly and atypical lymphocytosis (4). The majority of patients are between 15 and 24 years old. Systemic symptoms may be the clue to diagnosis with lethargy and malaise commonly prominent. Differentiation from group A streptococcal pharyngitis may be difficult since both may have thick, exudative tonsillitis and palatal petechiae. Not only are anterior and posterior chain lymph nodes in the neck enlarged, but axillary and inguinal adenopathy often occurs. The spleen enlarges in about 50% of cases and the liver enlarges in 10-15% but frank jaundice is seen in only about 5%. A rash is classically elicited by ampicillin (hence, amoxicillin as well), but may be seen in about 5% of patients who do not receive antibiotics. The complete blood count may show thrombocytopenia (sometimes marked but usually mild). Lymphocytosis, often with more than 10% atypical lymphocytes can been see on the differential (3). Testing for EBV can be done with a "Monospot" test that actually tests for heterophil antibodies in the patient's serum that agglutinate sheep or horse erythrocytes. The sensitivity is about 90%, but it is often much less in infants and children less than 4 years old. Although several drugs have activity against EBV, none are effective for routine use. The mainstay of treatment is symptomatic

management. Advice to avoid vigorous activities for one month after onset of illness will help protect against possibly fatal splenic rupture (3). Corticosteroids should only be used to prevent occlusion of the airway by enlarged tonsils or in other special cases such as massive splenomegaly, myocarditis, hemolytic anemia and hemophagocytic syndrome (4).

A final virus that deserves to be included in the differential is HIV. After a period of incubation ranging from 6 days to 5 weeks, fever, nonexudative pharyngitis, lymphadenopathy, lethargy, myalgia and arthralgia develop in acute HIV infection. The higher incidence of rash in acute retroviral syndrome (40-80% versus 5%) and the occurrence of mucocutaneous ulceration may help differentiate the above from infectious mononucleosis, which can have similar constitutional symptoms and sore throat. Diagnosis is further complicated by the fact that tests for HIV antibody are often negative during this time, so assays for p24 antigen or HIV RNA must be used if the diagnosis is suspected. The diagnosis is important to make because during this period, the patient benefits from maximal therapy with antiretroviral agents (3).

Group A streptococcal (GAS) pharyngitis is the most common bacterial cause of sore throat, comprising 15-30% of children's sore throats and a smaller percentage in adults (5-10%). GAS pharyngitis is treated to shorten the course slightly (only if treatment is initiated early), to avoid suppurative sequelae, which include peritonsillar or retropharyngeal abscess, cervical lymphadenitis, mastoiditis, otitis media and sinusitis and non suppurative sequelae which include acute rheumatic fever. Although there is no evidence that treatment of GAS pharyngitis prevents the development of post streptococcal glomerulonephritis, a course of systemic antibiotics, usually penicillin, is recommended in patients with the latter condition when the diagnosis is made. This is generally to prevent the spread of nephritogenic strains and it has not been shown that antibiotics alter the course of the glomerulonephritis (3). Both post streptococcal glomerulonephritis and acute rheumatic fever can result from pharyngeal GAS infection but with skin infection (impetigo) the only non suppurative sequelae is post streptococcal glomerulonephritis.

Rheumatic fever deserves special mention since it historically was so significant in the U.S. It continues to be a significant cause of morbidity and mortality in many populations of the world. Around the year 1900, rheumatic fever and its sequelae were the leading causes of death among school age children. Although known to be associated with sore throat, the lack of identification of streptococci in damaged heart valves and elsewhere puzzled investigators until about 1930 when the association between antibodies and their effect on various tissues involved in the illness began to be elucidated. First with sulfa and subsequently with penicillin, streptococcal pharyngitis has been treated successfully since World War II. The decline in the incidence of acute rheumatic fever over the past 100 years, however, began before the advent of antibiotic availability and has been attributed to a decrease in the rheumatogenicity of streptococci (5). Astute observations in the 1980s of similarities in areas of the brain affected in Sydenham's chorea and obsessive-compulsive disorder (OCD) and exacerbation of OCD with GAS infection led to interest in pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections ("PANDAS") (7). Research continues to accumulate in this exciting field related to this disease.

Discussion on how to diagnose GAS pharyngitis clinically has never been definitively settled. Certain factors such as the typical age group of school age children, exudative appearance of tonsils, anterior cervical adenopathy, appropriate season (mid-winter to early spring) and absence of rhinorrhea and cough make the diagnosis of GAS pharyngitis likely (60-70% in children and 20-30% in adolescents) (3,6). Recommendations for whom to test vary and are defined in detail in the Red Book (4). Examples of factors to consider include viral symptoms such as coryza (acute inflammation of nasal mucosa with discharge, i.e., a cold), conjunctivitis, stomatitis, hoarseness, or diarrhea which make GAS pharyngitis less likely, or prior history in the patient or a family member of nonsuppurative sequelae which should cause stronger consideration for testing. GAS pharyngitis in children below 3 years old is very uncommon (4).

A properly done throat culture, which includes vigorous swabbing of both tonsils and the posterior pharynx remains the best diagnostic test available with about a 90% sensitivity (3,4). Newer rapid streptococcal tests that measure group A streptococcal carbohydrate antigen in a few minutes, as opposed to the 24-48 hours for a throat culture, have gained in popularity but have sensitivities that are 80-90% at best. A negative rapid streptococcal test is recommended to be followed up with a throat culture in suspicious cases. Neither test will differentiate a carrier from a patient with an acute infection (3).

Since most throat infections end up having a viral etiology, it is difficult to explain why one study showed that 70% of children and adolescents seen for sore throats in primary care settings received antibiotics (8). A study in military recruits in the 1950s showed that there is a window of 9 days from onset of pharyngitis during which administration of antibiotics is effective to prevent acute rheumatic fever. Since acute GAS pharyngitis lasts only 2 to 5 days without treatment, this means that rheumatic fever can still be prevented after the symptoms of pharyngitis are gone (6). Penicillin remains the drug of choice and should be continued for a full ten days or given intramuscularly in the procaine/benzathine formulation. A recent study looking at enhancing compliance with once daily amoxicillin, showed amoxicillin to be as effective once daily as three times daily penicillin, the implications being clear for compliance (9). The effectiveness of once daily amoxicillin, however, for prevention of rheumatic fever remains to be defined. Possible reasons for treatment failure include compliance issues, re-exposure, co-pathogens and carrier status (6).

Different types of streptococci including serogroups C and G may also cause pharyngitis via food and waterborne routes of infection. Although these types may cause glomerulonephritis, they are not associated with acute rheumatic fever. The infections tend to be milder than those with group A streptococci. Treatment, however, is recommended when these organisms are identified in symptomatic patients although the proven benefits are unknown. The same antibiotics that are used for group A streptococci are effective for types C and G (3).

Arcanobacterium haemolyticum is a rare cause of pharyngitis that usually occurs in adolescents or young adults. The illness may mimic group A streptococcal infection including a scarlatiniform rash. Erythromycin is the drug of choice (3). Neisseria gonorrhoeae may cause a pharyngitis if inoculated into the pharynx by oral contact with infectious material. Usually, the infection is asymptomatic but clinical pharyngitis and tonsillitis may develop. Disseminated disease should be suspected if Neisseria gonorrhoeae is found. Special media is required if the diagnosis is suspected. The treatment is the same as for genital disease (ceftriaxone 125mg IM, or single dose oral quinolone such as ciprofloxacin 500mg or ofloxacin 400mg plus azithromycin 1gm single dose or doxycycline 100mg bid for seven days) (3).

Diphtheria is now a rare disease in the US with only a single case reported to the Centers for Disease Control in the last few years. This disease has historical significance in the US, but currently has ongoing morbidity and mortality in other areas of world such the central Asian republics, Russia and Ukraine (3,4). The characteristic finding is the grayish brown diphtheric pseudomembrane which may involve the tonsils unilaterally or bilaterally and can extend to involve the soft palate, nares, pharynx, larynx or even the tracheobronchial tree (3). Case fatality rates range from 3% to 23%, the usual mechanisms of morbidity and mortality being upper airway obstruction from extensive membrane formation and myocarditis. Peripheral neuropathy may also occur (4). Edema of the soft tissues in the neck and prominent cervical and submental adenopathy may give the patient a "bull-neck" appearance (3). The disease is best prevented by

immunization, but if necessary, is treated with equine antitoxin and antibiotics, erythromycin or penicillin G intravenously. Antimicrobial therapy alone is not a substitute for antitoxin (4).

Mycoplasma pneumoniae may cause pharyngitis, but since it is also commonly isolated from controls, the significance of such infections remains unknown. Chlamydia pneumoniae has also been reported to cause pharyngitis either by itself or preceding a pneumonia. Since routine testing does not diagnose either of these organisms, treatment is not likely to be offered. The incidence of these organisms is likely seen in only a small percentage of infections and since serious complications are not commonly observed, it is likely that these infections resolve without treatment in most instances. (3,6)

Peritonsillar abscess is one of the listed suppurative sequelae of group A streptococcal infection but may also occur as a result of infection from other oral anaerobes. Acute tonsillopharyngitis precedes the formation of abscess, usually with an afebrile period noted or unresolving fever before the onset of severe throat pain. There may be trismus (pain on opening the mouth) and refusal to speak or swallow because the pain may be so intense. On exam, one of the tonsils is usually markedly swollen, with effacement of the anterior tonsillar pillar and deviation of the uvula to the opposite side. Untreated abscesses may rupture into the airway. Treatment involves incision and drainage of the abscess and intravenous antibiotics. Penicillin may be used although some prefer clindamycin for better anaerobic coverage. Without a history of chronic tonsillitis, there is a 10% recurrence rate. Authorities vary on whether tonsillectomy should be performed after the initial episode (2,10).

Retropharyngeal abscess can also manifest as a complication of bacterial pharyngitis or less commonly from extension of vertebral osteomyelitis or penetrating injury to the posterior pharynx. The potential space between the posterior pharyngeal wall and the prevertebral fascia contains lymphatic tissue that involutes around age 3 to 4 years, making infection less common after that age. A child with a preceding acute nasopharyngitis or pharyngitis who refuses to eat, has high fever, severe distress, hyperextension of the neck or noisy gurgling respirations may have a retropharyngeal abscess. Imaging (lateral neck radiographs) is essential to confirm the diagnosis, although in an uncooperative child, a bulge in the posterior pharynx may be seen. To obtain a proper soft tissue lateral neck x-ray, the neck should be in full extension (lordotic) and the x-ray should be taken in end-inspiration. False positive x-rays (false widening of the prevertebral soft tissue) may occur with poor positioning. Untreated retropharyngeal abscesses may rupture into the airway or spread down the fascial planes to the mediastinum. Treatment includes incision and drainage under general anesthesia and empiric intravenous antibiotics with coverage for Staphylococcus aureus until culture and sensitivity information is available (2,10). A "cold" abscess with tuberculosis may present as a retropharyngeal abscess (11).

Candida may cause infection of the pharynx under conditions of altered immunity such as HIV infection, immunodeficiency or diabetes (11). Thrush (mild oral candidiasis) is common in healthy infants. White plaques may be seen on the buccal mucosa and the tongue. Initial treatment is with oral nystatin.

Mechanical problems such as tonsillar hypertrophy leading to obstructive sleep apnea and chronic mouth breathing may cause pharyngitis. Foreign body must always be included in the differential of sore throat that does not appear infectious. Asymmetric swelling of the tonsils without infection may be a clue to malignancy (2,11). Adult type epiglottitis should be considered in older children and teens complaining of a severe throat without much clinical findings.

Diagnoses such as chronic fatigue syndrome contain sore throat as part of their criteria but continue to be controversial. Emerging entities such as periodic fever syndrome (PFAPA) which include sore throat (pharyngitis), fever, aphthous stomatitis and adenopathy in the cervical region may be more common that initially thought (12). The latter symptoms occur for 3 to 6 days with three weeks during which the patient is entirely well interspersed with clockwork periodicity. As one author puts it, is periodic fever an infectious disease or immune dysregulation? The answer is easy: no one knows (13).

Pharyngitis can have a myriad of causes, but for the most part, the causes are easily managed viral infections. The physician has to have a certain awareness of the more serious problems which can present as pharyngitis and the appropriate workup and management once the diagnosis is suspected. Certain clues can help the physician diagnose the more serious causes of sore throat and treat them appropriately.

Questions

1. A 12 year old male with 4 days of sore throat comes into the office. He has been afebrile, has rhinorrhea, cough and one day of diarrhea associated with his sore throat. The throat is mildly erythematous with otherwise normal appearing tonsils. The best course of action is (this may be a controversial question depending on your practice setting):

a. Swab his throat and give a 10 day course of antibiotics, you will call him if the culture is negative for group A strep so that he can stop antibiotic treatment.
b. Swab his throat, withhold antibiotics unless his culture is positive.
c. Advise him on symptomatic treatment.
d. Give him antibiotics without testing for group A strep.

2. A 14 year old boy who you know is homeless and possibly engaging in prostitution comes into clinic complaining of sore throat, rash and pronounced fatigue. One exam, he has an exudative pharyngitis. Tests to consider include (choose all that apply):

a. Throat swab for group A strep
b. HIV test for antibody
c. Throat swab for Neisseria gonorrhoeae
d. Monospot for EBV infection

3. A 3 year old is very fussy, febrile and has profuse rhinorrhea. On exam, shallow ulcers are noted on the soft palate and vesicles are noted on one palm and both soles of the feet. The etiology of this infection is likely:

a. Group A streptococci
b. Arcanobacterium haemolyticum
c. Coronavirus
d. Coxsackievirus

4. A 6 year old child recently adopted from somewhere in Russia complains of sore throat and is noted by the parents to have a lot of "grayish junk" in his mouth and nose. Exam shows an adherent grayish-white membrane over both tonsils and the soft palate that, when removed, leaves an edematous, bleeding area of tissue. After calling your state health department, you initiate therapy with:

a. Intravenous erythromycin or penicillin G.
b. The above antibiotics plus antitoxin.
c. Antitoxin alone.
d. IVIG.

5. In children, nonsuppurative sequelae of group A strep infection of the pharynx include (circle all that apply):

a. Post streptococcal glomerulonephritis.
b. Acute rheumatic fever.
c. Periodic fever syndrome.
d. PANDAS (maybe).

Related x-rays

Case of retropharyngeal abscess compared to croup and epiglottitis: Boychuk RB. Drooling, Stridor, and a Barking Cough: Croup?? In: Yamamoto LG, Inaba AS, DiMauro R. Radiology Cases In Pediatric Emergency Medicine, 1994, volume 1, case 10. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v1c10.html

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Answers to questions

1. any of the answers may be correct depending on your practice setting.
   a. for difficult to reach families or someone you don't trust to follow up.
   b. is probably what you would do for most families you felt comfortable with follow up (i.e., you could reach them on the phone if you needed to).
   c. is what you might do if you are playing the odds; it's probably viral.
   d. is what you might do during an epidemic.
2. a, c and d (b - HIV antibody test - is usually negative during this period and PCR for p24 antigen, RNA or reverse transcriptase is required).
3. d
4. b (antitoxin must be given with antibiotics)
5. a, b and d (no one is sure what causes PFAPA)

Chapter VI.10. Pertussis
Leo U. Pascua, MD

In December, a 2 year old female presents to the office with a chief complaint of afebrile nocturnal coughing for 3 days. Her past medical history is significant for atopic dermatitis (uses topical hydrocortisone), as well as multiple visits for wheezing episodes which respond well to nebulized albuterol. Gastroesophageal reflux had been explored and ruled out based on history. The family history is positive for maternal, paternal and sibling asthma. She is a recent immigrant and may not have had all her immunizations.

Exam: VS T37.0, P110, R40, BP 100/60, oxygen saturation 97% in RA. All growth parameters are at the 10th percentile. She is somewhat tired and clingy but alert. HEENT significant for mild nasal congestion. Heart regular without murmurs. Extensive and diffuse biphasic wheezing is heard in the lungs. Occasional coughing is heard in the office during the clinic visit. No flaring, retractions or cyanosis is observed. She has lichenified skin over her extremities.

A presumptive diagnosis of reactive airway disease is made, and he is discharged to home on oral albuterol and prednisone. She returns 2 days later, without much improvement. A CXR is unremarkable. Amoxicillin is empirically added to her regimen. She returns 2 days later with increased coughing and tachypnea with an oxygen saturation of 94% in room air. A repeat CXR shows a suggestion of a RLL infiltrate. A presumptive diagnosis of pneumonia is made and she is admitted to a general hospital for further evaluation and management of pneumonia and asthma exacerbation. CBC is normal. RSV ELISA and pertussis fluorescent antibody from the nasopharynx are negative. A pertussis culture is obtained. She improves and is discharged home in 3 days on amoxicillin/clavulanate.

She returns to the office 3 days later with increasing coughing and hypoxia (oxygen saturation 92%). She is admitted to a tertiary care hospital for management. An RSV ELISA and pertussis fluorescent antibody are again negative. Her earlier pertussis culture is negative. An infectious disease consult is obtained. Based on her clinical presentation of hypoxia and repetitive coughing; a working diagnosis of pertussis is made. Erythromycin and supportive care are initiated. A report is made to the Department of Health. Household contacts are subsequently interviewed, and erythromycin prophylaxis is started in all contacts.

After 7 days, she improves and is discharged to home to complete her course of erythromycin.

Bordetella pertussis is a gram negative coccobacilli that is the cause of an acute respiratory illness initially characterized by protracted coughing. With respect to the differential diagnosis, protracted coughing can also be caused by Mycoplasma, parainfluenza or influenza viruses, enteroviruses, respiratory syncytial virus, or adenoviruses. The majority of cases occur from July through October. Pertussis is extremely contagious, with attack rates as high as 100% in susceptible individuals exposed to aerosol droplets at close range. Day care centers have the potential for high exposure rates. B. pertussis does not survive for prolonged periods in the environment. Although a person may be fully immunized, either actively or passively, the rate of subclinical infection is as high as 50%. Neither natural disease nor vaccination provides complete or lifelong immunity against reinfection or disease (1). Protection against typical disease begins to wane 3-5 years after vaccination and is unmeasurable after 12 years. Adults in the United States, e.g., day care center operators, baby-sitters, etc., have inadequate antibody to B. pertussis (2).

B. pertussis produces an array of biologically active substances which are responsible for attachment to ciliated respiratory epithelial cells, inhibited clearance of organisms and local epithelial damage. In addition, pertussis incites histamine sensitivity, insulin secretion and leukocyte dysfunction. There are 3 post-incubation stages: 1) catarrhal, 2) paroxysmal, and 3) convalescent.

After an incubation period from 3 to 12 days, the catarrhal stage is marked by: congestion, rhinorrhea, low-grade fever, sneezing, and lacrimation. As symptoms wane, the paroxysmal coughing stage begins which can be characterized by one or more of the following: 1) Intermittent, irritative hacking paroxysmal coughing, 2) Choking, gasping, eyes watering and bulging, 3) Occasional coughing up of mucous plugs, 4) Post-tussive exhaustion, 5) Coughing in long spasms with the face turning red, or sometimes blue. The coughing wanes and improves during the convalescent stage. Each stage lasts about 2 weeks. However, immunized children do better, with shortening of all stages. Conjunctival hemorrhages and petechiae on the upper body are common due to all the coughing,

Pertussis should be suspected in a patient who complains of incessant coughing for 2 weeks, especially if nothing else shows up on the physical exam. Fever, sore throat, and conjunctivitis usually accompany adenoviral infections. Mycoplasma usually has a history of fever, headache, and rales. Chlamydia trachomatis presents with purulent conjunctivitis, tachypnea, rales or wheezes. Leukocytosis (normal small cells, rather than the large atypical lymphocytes seen with viral infections) due to absolute lymphocytosis occurs in the late catarrhal and paroxysmal stages. Neutrophilia would suggest a different diagnosis or secondary bacterial infection.

The chest radiograph shows perihilar infiltrates or edema and variable degrees of atelectasis. Parenchymal consolidation also suggests secondary bacterial infection. Pneumothorax, pneumomediastinum, and air in soft tissues sometimes occur. Isolation of B. pertussis in a culture is the gold standard and is a more sensitive and specific method of diagnosis than direct fluorescent antibody (DFA) testing of nasopharyngeal secretions. Cultures are positive during the catarrhal stage and escalating paroxysmal stage. However, a false negative can occur in those who have received amoxicillin or erythromycin. A flexible swab kept in the posterior nasopharynx until the patient coughs, is one way to obtain the specimen. DFA testing of nasopharyngeal secretions is rapid, but is highly dependent on the experience of the lab technician.

Infants under 6 months of age have a higher morbidity and mortality risk. Those under 2 months of age have the highest reported rates of pertussis-associated hospitalization (82%), pneumonia (25%), seizures (4%), encephalopathy (1%), and death (1%). The principal complications of pertussis are: apnea, secondary infections (such as otitis media and pneumonia), and physical sequelae of forceful coughing.

PICU care with artificial ventilation is usually limited to infants under 3 months of age, and is suggested with the presence of apnea and cyanosis. Secondary bacterial pneumonia (Staphylococcus aureus, S. pneumonia, mouth flora) is another cause for admission and his heralded by fever, tachypnea, respiratory distress between paroxysms, and absolute neutrophilia.

Coughing transiently increases the intrathoracic and intra-abdominal pressure resulting in conjunctival hemorrhages, petechiae on the upper body, epistaxis, hemorrhage in the central nervous system and retina, pneumothorax and subcutaneous emphysema, and umbilical and inguinal hernias.

CNS abnormalities occur and are almost always the result of hypoxemia and hemorrhage associated with coughing or apnea in young infants (due to laryngospasm, vagal stimulation just before a coughing episode, from obstruction during an episode, or from hypoxemia following an episode). Seizures are usually the result of hypoxemia. Also, pneumonia can precipitate SIADH, resulting in hyponatremic seizures.

Reversible bronchiectasis or pseudobronchiectasis occurs commonly after pertussis. The bronchi may appear cylindrically dilated on bronchography, but usually resolved in about 4 months.

Patients with significant respiratory infections should be hospitalized if they are less than 3 months of age, (other causes of pneumonia presenting during the first weeks of life include C. trachomatis, genital Mycoplasma, Ureaplasma urealyticum, and occasionally bacteria such as Haemophilus species, streptococci, and Bordetella pertussis. Other indications for hospitalizations include: severe coughing paroxysms, cyanosis, poor social support, or an infection in a high risk patient (prematurity, cardiac disease, chronic pulmonary disease, neuromuscular disorder, etc.).

Admission orders should include:

Cardiorespiratory monitoring, continuous pulse oximetry, apnea monitor.

Detailed cough records (cyanosis, tachycardia, bradycardia, presence of coughed up mucus plug; post-tussive exhaustion and/or unresponsiveness).

Documentation of feeding, vomiting, and weight change.

Prn oxygen, stimulation, or suctioning (note: suctioning of nose, oropharynx, or trachea always precipitates coughing, occasionally causes bronchospasm or apnea, and should be done prn only).

Avoidance of large volume feedings.

Medication order should include: erythromycin (estolate form preferred) 40-50 mg/kg/day div qid (max 2 g/day 24 hr) x 14 days.

Nursing orders should include:

Respiratory isolation for at least 5 days after start of erythromycin.

Restricting visitation of coughing family members who might be spreading pertussis to others in the hospital (until they have taken erythromycin for 5 days).

Management orders of household close contacts should include:

Erythromycin, 40-50 mg/kg/day divided qid (max 2 g/day 24 hr) for 14 days to all household and close contacts, i.e., day care, regardless of age, history of immunization, or symptomatology.

Pertussis-containing vaccine to all unimmunized contacts younger than 7 years.

Hospital discharge criteria should include clinical improvement plus: no intervention required during coughing, adequate nutrition, absence of complications, and the parents are prepared for further home care.

Primary prevention with pertussis vaccine is key. The vaccine currently used in the primary immunization series is a safer acellular vaccine composed of a suspension of inactivated B. pertussis, combined with diphtheria and tetanus (DT) toxoids and aluminum-containing adjuvants (DTaP vaccine).

For historic purposes, the adverse effects of the older whole cell vaccine (DTP, which is no longer used) are mentioned below. It resulted in more frequent pain, swelling, erythema, and systemic reactions, such as fever, fretfulness, crying, drowsiness, and vomiting. Febrile seizures, albeit rare, occurred within 48 hr and were brief, generalized, self-limited, and occurred more commonly in those with a history of seizures. Collapse or shock-like state (hypotonic-hyporesponsive episode) was rare, uniquely associated with pertussis vaccine, and has no permanent neurologic sequelae. Very rarely, pertussis vaccine was associated with acute neurologic illness in children who were previously normal. Severe adverse events, such as death, encephalopathy, onset of a seizure disorder, developmental delay, or learning or behavioral problems, have occurred in individuals temporally associated with pertussis immunization or alleged to be causally associated. These adverse effects are less likely to occur with the generation of the currently used acellular vaccine (DTaP), which has supplanted the DTP series.

Some parents have refused pertussis vaccine because of its adverse effects. Many parents believe that herd immunity will protect their children. The concept of herd immunity is that if 99% of the population is immune, then the infection can never find enough susceptible hosts to sustain itself and the few susceptible individuals within the population are unlikely to be exposed to the infection. However, herd immunity does not apply to pertussis since pertussis immunity declines substantially with age. Most teens and adults are susceptible, even if they were immunized as children. Although teens and adults with pertussis will manifest with only mild to moderate respiratory symptoms, they represent a large population of susceptible individuals who can sustain an epidemic, and thus expose unimmunized infants and children, who may have more severe infections and complications.

Questions

1. In the case, the patient's presentation and clinical course were consistent with pertussis, yet the pertussis culture was negative. Why?
   a. A false negative can occur in those who have received amoxicillin.
   b. A false negative can occur in those who have received albuterol.
   c. A false negative can occur in those who have a history of asthma.
   d. Direct fluorescent antibody (DFA) testing of nasopharyngeal secretions is the gold standard and is a more sensitive and specific method of diagnosis than culture.
   e. Cultures usually become positive only during the latter convalescent phase.

2. What etiology of sudden onset of coughing in an active infant can be effectively ruled out with a CXR?
   a. Mycoplasma
   b. Parainfluenza
   c. Enterovirus
   d. Respiratory syncytial virus
   e. Foreign body aspiration
   f. None of the above

3. Match the clinical manifestation to the disease process

a. Fever, sore throat, and conjunctivitis	1. Mycoplasma
b. Fever, headache, and rales	2. Adenovirus
c. Purulent conjunctivitis and tachypnea	3. Chlamydia
d. Choking, gasping, eyes watery and bulging.	4. Pertussis

4. An experienced ward nurse asks you to correct an admission order for pertussis. Which component is incorrect ?
   a. "Continuous cardiorespiratory monitoring".
   b. "Document episodes of cyanosis or post-tussive exhaustion".
   c. "Daily weights".
   d. "Deep suctioning q 3h".
   e. "Instruct parent regarding maximal size of feedings.

5. Case management dilemma scenario: You are the admitting intern on the wards. It is 3 PM on a Friday afternoon. A patient is transferred from a neighbor island with a diagnosis of pertussis, complete with positive direct fluorescent antibody (DFA). The summary of PE findings by the community PMD includes petechiae on the upper body, epistaxis, and umbilical hernia. Upon admission to the ward you repeat the physical exam and also note retinal hemorrhages, which are confirmed by an ophthalmologist who just happens to be around. The parents have returned to the neighbor island for the weekend to fulfill important obligations and have already made arrangements to return on Monday. Given the presence of retinal hemorrhages, do you make a referral to Child Protective Services?

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Answers to questions

1.a. A false negative can occur in those who have received amoxicillin.

2. None of the choices are correct. Choices a and e are the closest to being correct, but technically, these answers are incorrect. Mycoplasma pneumonia might show up as a pneumonia on a CXR, but this would be non-specific for mycoplasma. Additionally, some mycoplasma infections may not cause a pneumonia. Foreign body aspiration might show up on a CXR, but these often require special views such as an expiratory view or a lateral decubitus view. Foreign body aspiration is frequently occult.

3. a-2, b-1, c-3, d-4

4.d. Suctioning of nose, oropharynx, or trachea always precipitates coughing, occasionally causes bronchospasm or apnea, and should be done prn only.

5. Increased intrathoracic and intra-abdominal pressure during coughing can result in conjunctival hemorrhages, petechiae on the upper body, epistaxis, hemorrhage in the central nervous system and retina, pneumothorax and subcutaneous emphysema, and umbilical and inguinal hernias. A child protective services report is not necessarily indicated since pertussis could cause this. Other clinical or psychosocial findings inconsistent with pertussis may lead one to report this to child protective services.

Chapter VI.11. Pulmonary Infections
Kimberly N. Otsuka, MD

A previously healthy 4 year old boy is brought to an urgent care center by his mother for difficulty breathing for one day. Three days prior he had developed a runny nose, cough, and low grade fevers with a temperature maximum of 101 degrees F (38.3 degrees C). He continued to take liquids well, but his solid intake has decreased. His temperature this morning was 103 degrees F (39.4 degrees C) and he was breathing fast and working hard to breathe. He does not have any ill contacts. He has never been hospitalized or had any surgeries. He was born at term without any complications. He is not taking medications other than acetaminophen. His immunizations are up to date for his age (except he had not received the pneumococcal conjugate vaccine). His parents and 10 year old sister are healthy and the remainder of his family history is non-contributory. There are no smokers in the household, and he has not traveled recently. He does not have a history of choking or vomiting. He has not had frequent ear or skin infections. He does not have a history of foul-smelling stools.

Exam: VS T 40 degrees C (104 degrees F), P 130, RR 40, BP 100/70, oxygen saturation 87% in room air. His height and weight are in the 50th percentile for his age. He is awake and alert, in moderate distress. His conjunctiva and TMs are normal. His nasal mucosa is erythematous with yellowish discharge. His lips and mucous membranes are dry. His neck is supple, with several small anterior cervical lymph nodes. Lungs: Moderate subcostal, intercostal, and supraclavicular retractions, symmetric expansion, dullness to percussion at the right base, increased vocal fremitus over the right base, decreased air entry over right lower lobe with crackles, no wheezes. Heart: Tachycardia, regular rhythm without murmur. Pulses are 2+, and capillary refill time is 3 seconds. His abdomen, skin, and neurological examinations are unremarkable.

CBC WBC 20,000, 70% segs, 11% bands, 15% lymphs, 3% monos, 1% eos. Hemoglobin 12.4, platelet count 280,000. Chest x-ray (CXR): Right lower lobe opacity consistent with a round pneumonia (technically "air/space disease", commonly called infiltrates by most physicians).

Because of the hypoxia, he is given supplemental oxygen (with subsequent improvement in oxygen saturation), as hospitalization arrangements are made. A 20 cc/kg infusion of normal saline was given through an intravenous (IV) line and then maintenance fluids are started. A blood culture is obtained and he is started on IV cefuroxime. He improves over the next day. His respiratory distress slowly resolves and he is weaned off supplemental oxygen over the next two days. His blood culture shows no growth. He is discharged home on high dose amoxicillin for a total of 10 days of therapy. His discharge diagnosis is probably pneumococcal pneumonia.

Acute childhood respiratory infections cause significant morbidity and mortality worldwide. Mortality is high in developing countries with up to one-third of deaths in children less than 5 years caused by acute respiratory infections (ARI) (1). The disparity in mortality is due to the severity of infection (perhaps due to differences in nutrition, overall health, immunization practices, and medical care availability) since the incidence of acute respiratory infections is similar between developed and developing countries with infants experiencing about 4-8 episodes per year (1). In the US, mortality from ARIs has declined since 1968 (1,2).

There are 2 basic classification systems used for acute respiratory tract infections: the case-management classification system used by the World Health Organization (WHO) and the "traditional" clinical classification system (1). The case management system divides ARIs by symptoms (i.e., stridor, wheezing, and no wheezing) and their severity (i.e., mild, moderate, severe, and very severe). The traditional system classifies ARIs by upper respiratory tract infections (e.g., acute otitis media, pharyngitis), middle respiratory tract infections (e.g., croup and epiglottitis), and lower respiratory tract infections (e.g., bronchiolitis, bronchitis, pneumonia). Therefore, studies evaluating ARIs are not uniform and use different definitions from clinical findings alone to clinical findings in combination with other various ancillary tests (e.g., chest radiography).

Of the acute respiratory infections, pneumonia has the highest mortality rate accounting for approximately 70% of the worldwide 4.5 million deaths from acute respiratory infections (4). Although mortality from pneumonia in children in the United States has declined by 97% between 1939 and 1996 (5), pneumonia continues to be a leading cause of morbidity in children. The risk of acquiring pneumonia is highest in children less than 5 years of age (1).

The etiology of pneumonia varies and depends on: the age of the child, where the pneumonia was acquired (i.e., community vs. nosocomial), local epidemiology (e.g., influenza epidemics), host factors (e.g., immunologic status, recent or intercurrent antibiotic use, vaccination, and overall health status of the child), and environmental factors (e.g., travel, season of the year, daycare, or crowded living conditions) (4,6-9). Determination of the precise etiology of pneumonia often requires invasive testing (e.g., lung biopsy), and therefore, this is done infrequently. Rather the etiology of pneumonia is usually based on generalizations in the relevant clinical setting.

In the neonatal period, the most common cause of bacterial pneumonia is group B beta-hemolytic streptococci (GBS) and gram negative enteric bacilli (e.g., E.coli), the same organisms associated with neonatal sepsis (4). In infants and children outside of the neonatal period, viruses are the most common cause of pneumonia (4,6,10-11) and respiratory syncytial virus (RSV) is one of the most common causes in infancy, especially in premature infants (9,12). Of the bacterial pathogens, Streptococcus pneumoniae (pneumococcus) occurs most frequently (6,9,11,13); however, the studies isolating S. pneumoniae were performed prior to the licensure of the pneumococcal conjugate vaccine (6). Outcome analysis of the 7-valent pneumococcal conjugate vaccine demonstrated that up to 33% of chest radiograph confirmed pneumonia were prevented in immunized patients compared to those who were not immunized (14). Therefore, a different bacterial pathogen may supersede S. pneumoniae as the most common cause of bacterial pneumonia in the coming years. Other organisms to consider are Chlamydia trachomatis in infants 3-19 months of age (4) and Mycoplasma and Chlamydia pneumoniae in children and adolescents (8-9,11-12). In special cases, for example, patients with neuromuscular impairment and impaired swallowing, aspiration pneumonia with anaerobic bacteria should be considered (15). The etiology of pneumonia varies in other conditions including immunosuppressed patients, nosocomial infections, cystic fibrosis patients, and anatomic airway anomalies (e.g., tracheostomies). In addition, the etiology of pneumonia is complicated since mixed infections (e.g., viral-bacterial) can occur in 16-34% of patients (7,11,13).

The lower respiratory tract in healthy persons is sterile (16). Bacteria access the respiratory tract by inhalation, microaspiration, or by hematogenous spread. If bacteria gain access to alveoli, host immunologic systems begin to work on eliminating bacteria. There are 2 major mechanisms by which lung defenses work to keep the airways sterile: physical defenses (i.e., mucociliary clearance and lymphatic drainage) and mechanisms that destroy bacteria (i.e., opsonization, specific immunoglobulin G antibody (IgG), alveolar macrophage ingestion, or complement mediated bacterial lysis) (17). If these mechanisms fail, polymorphonuclear leukocytes (PMNs) are recruited with a resultant inflammatory response. Perpetuation of this inflammatory response leads to pneumonia. There are 4 major histologic

steps seen in pneumococcal pneumonia described by Tuomanen, et al (18): engorgement, red hepatization, grey hepatization, and resolution. Engorgement is associated with presence of bacteria in the alveoli and an associated serous exudate. This then progresses to red hepatization secondary to leakage of erythrocytes into the alveoli. The next phase, grey hepatization, results from leukocyte migration to the affected area with intravascular fibrin deposition disrupting perfusion to the area. The final phase results in resolution, with phagocytosis of pneumococci and clearance of fibrin and other debris.

Outside of the neonatal period, pneumonia is suspected in patients with clinical signs and symptoms suggestive of impairment of the lower respiratory tract. Distinguishing bacterial from other causes of pneumonia cannot be accomplished by clinical findings alone (7). Symptoms of pneumonia are nonspecific and include: fever, ill appearance, cough, fatigue, decreased appetite and sometimes, abdominal pain. Signs of lower respiratory tract involvement include: tachypnea (greater than 50 breaths/minute in children less than 12 months, and greater than 40 breaths/minute for older children) (4), cyanosis, increased work of breathing (i.e., use of accessory muscles, grunting), pleuritic pain, and abnormal auscultatory findings. These signs do not differentiate a viral from bacterial process. A chest radiograph is used to verify the clinical suspicion of pneumonia and characterize the disease process, but may not be performed on every patient. Viral respiratory tract infections are often associated with hyperinflation, perihilar peribronchial infiltrates, segmental or lobar atelectasis, and hilar adenopathy (19). Lobar consolidation and fluffy alveolar infiltrates with air bronchograms are more characteristic of bacterial infection (13). However, there is overlap between these two groups (13). Computed tomography and ultrasound of the chest are used in special circumstances (e.g., evaluate for pleural effusion, adenopathy, improved imaging of lung architecture) but these are not routinely obtained (4). Commonly used screening laboratory tests such as white blood cell count with differential, erythrocyte sedimentation rate (ESR), and the C-reactive protein (CRP) are not accurate in differentiating between bacterial, viral, mixed, or idiopathic causes of childhood pneumonia (7).

Determination of precise etiology of pneumonia is difficult due to the lack of sensitive and specific tests. Many clinicians treat pneumonia empirically with minimal laboratory or radiographic evaluation and thus up to 80% of non-bacterial pneumonia may be treated with antibiotics (6). This approach is satisfactory when clinical risk is deemed to be low. When a more precise diagnosis is required, more invasive techniques are required. Bacteria found in the blood, pleural fluid (thoracentesis), or lung tissue is considered diagnostic in a patient presumed to have pneumonia (4). Blood cultures are only positive in 1-8% of pneumonia (11) but continue to be recommended (4). Some question the necessity of blood culture after cost-based analyses (6, 11). Transthoracic needle aspirates, transtracheal aspirates, and open lung biopsy (the gold standard for diagnosis) are rarely performed due to the risk involved for these procedures (11,20), except in severe cases or in immunocompromised hosts (4). Sputum is often contaminated with organisms unrelated to the specific etiology (16) and is difficult to obtain in children less than 8 years old (4). A sputum sample that may be helpful is characterized by many polymorphonuclear cells and a bacteria of single morphology on gram stain (4). Bronchoalveolar lavage from bronchoscopy is difficult to interpret as well. The results are non-specific (i.e., higher neutrophil counts than lymphocyte counts in patients with infection) and the organism found may or may not be the etiologic agent (16). Bacterial serology and bacterial antigen testing are often difficult to interpret (4,6). Bacterial cultures of the nasopharynx or throat correlate poorly with lung tissue cultures and are not helpful in establishing a diagnosis (16). Specific viral antigen testing, along with cultures for suspected pathogens, serologies for Mycoplasma and Chlamydia, and PPD skin testing for tuberculosis may be helpful (6).

Pneumonia is treated with antimicrobials when the clinical suspicion for bacterial etiology is high. Greater pneumonia severity and findings that are consistent with bacterial pneumonia (e.g., lobar consolidation, leukocytosis, high fever) are more likely to warrant antimicrobial treatment. Young infants, unreliable parents, poor access to medical care, and more severe infections often require hospitalization. Treatment of pneumonia is often empirically based and thus, information on antibiotic resistance patterns and mechanisms of resistance is important to determine the most appropriate treatment. For S. pneumoniae, the most common mechanism of resistance to penicillins is alteration of penicillin-binding sites that can be overcome with higher doses of the drug (6). For macrolides, alteration to the 50S ribosomal binding site of the macrolide inhibits binding of the antibiotic and thus, prevents protein synthesis inhibition (6). In addition, there is also an increase in efflux pumps for macrolides and this property can be overcome by using macrolides that achieve high tissue concentrations at the site of infection (e.g. azithromycin) (6). Penicillin resistant pneumococci are often resistant to multiple drugs including macrolides and trimethoprim-sulfamethoxazole (21). Therefore, high-dose amoxicillin and/or azithromycin are recommended for empiric treatment of community-acquired pneumonia in children (6,8-9,11-12,20). Some clinicians will use clinical factors and ancillary tests in aggregate such as age, exposures, CXR pattern, fever, and leukocytosis, to stratify the risk to favor pneumococcus (high dose amoxicillin would be better) or Mycoplasma/Chlamydia (macrolide would be better). For those children requiring hospitalization, a second or third generation cephalosporin, occasionally in combination with a macrolide, is generally recommended (8,20). Most treatment regimens are continued for a total of 7-14 days although this is based on little evidence (4).

Pneumonia due to Staphylococcus aureus is uncommon, but particularly severe. S. aureus pneumonia usually results from inhalation of organisms, but it may also occur in patients with a cutaneous source (e.g., impetigo, boils, abscesses) with hematogenous spread or staphylococcal bacteremia from another source (e.g. osteomyelitis, central line infection). If S. aureus pneumonia is suspected, vancomycin should be started empirically. Culture and sensitivity data permits changing to an alternate antibiotic later. Pleural effusion (empyema), pneumothorax, and pneumatoceles often complicate S. aureus pneumonia.

Pleural effusions can be classified in several ways. They can be a transudate or an exudate based on their protein content. A subpulmonic effusion versus an empyema is more clinically relevant. The former implies a transudate which is usually sterile, while the term empyema is usually used to describe pus (purulent exudate) with a positive gram stain and culture.

The overall outcome in children with pneumonia is excellent. The majority of children will recover without complications (11). Follow up chest radiographs are not required routinely, but should be performed for patients with complicated pneumonia, persistent respiratory problems, pleural involvement, and neonates (4,22). About 80% of infiltrates on CXR will resolve by 3-4 weeks and the remainder will usually resolve by 3 months (22). Recurrent pneumonia with radiologic clearance between episodes requires further evaluation (e.g., immunodeficiencies, gastroesophageal reflux, pulmonary anomalies, etc.) (4).

Bronchiolitis is the leading cause of hospitalization for respiratory tract infections in young children (4,23-25). Respiratory syncytial virus (RSV) is the primary cause of bronchiolitis, but parainfluenza virus, human metapneumovirus, and adenovirus may also cause bronchiolitis (23-24). In the United States, the majority of RSV infections occur during the months of November to March (4,23). RSV infections account for a significant amount of morbidity and health care expense in the young age group (24).

RSV is transmitted by direct contact with large droplets or fomites. Transmission can be limited by good handwashing (23). RSV bronchiolitis results from the spread of RSV to the lower respiratory tract after an incubation period 2-8 days where the virus undergoes replication in the nasopharynx (23). The infection results in infiltration of the respiratory epithelium with resultant inflammation and

necrosis, sloughing of the epithelium and increased mucus production causing airflow limitation in the small airways leading to the hallmarks of the disease (23). Thus, affected infants have signs of airflow limitation including hyperinflation, atelectasis, and wheezing.

The diagnosis is often made on clinical grounds during the RSV season. Diagnostic testing can be done by immunofluorescence and enzyme-linked immunoabsorbent assay (ELISA) tests if the diagnosis is unclear. Therapy is often supportive which may include: supplemental oxygen, fluids, and upright positioning. Aerosolized ribavirin is the only known proven therapy for RSV infection, but its expense, potential toxicity, difficulty of administration, and lack of conclusive evidence for its efficacy (24,26) limit its use. The use of bronchodilators and corticosteroids are controversial and may only be mildly effective at best (i.e., not been proven to be highly efficacious) (24-26). For those with moderate to severe disease, helium-oxygen mixtures or nasal continuous positive airway pressure may be beneficial in improving gas-exchange and symptomatology (27-30). Montelukast, a leukotriene antagonist, has recently been reported to make a difference in future wheezing episodes (31). Prophylaxis with palivizumab (RSV monoclonal antibody) or RSV-IVIG is given to select pediatric populations recommended by the American Academy of Pediatrics during RSV season to reduce RSV infection risk (32). Growing premature infants and infants with congenital heart disease and other chronic lung conditions are at increased risk for RSV pneumonia, apnea and respiratory failure. Healthy term infants with RSV usually develop mild bronchiolitis. Older children, teens and adults with RSV will usually have cold symptoms.

Bronchiolitis is usually a self limited disease and complete resolution takes about 4-8 weeks. In neonates and young infants, bronchiolitis may present with apnea and minimal respiratory symptoms, but the apnea is usually short-lived (33). Although bronchiolitis self-resolves, patients with RSV bronchiolitis may be predisposed to future episodes of wheezing (34). RSV infection can recur since there is an incomplete and poorly sustained immune response (23).

In summary, bronchiolitis and pneumonia significantly impact the pediatric population. Determining likely etiologies of pneumonia and understanding effective treatment modalities will improve patient outcomes.

Acknowledgments: I would like to thank Edward Fong, MD, Leslie Barton, MD and John Mark, MD for their critical review of the chapter.

Questions

1. Which of the following is the most common cause of pneumonia outside of the neonatal period?
    a. S. pneumoniae
    b. Mycoplasma
    c. Viruses
    d. Chlamydia

2. S. pneumonia resistance to penicillins is due to:
    a. Production of beta-lactamase
    b. Alteration of penicillin binding proteins
    c. Increased efflux pumps
    d. Low tissue bioavailability

3. True/False: Nasopharyngeal and throat cultures are useful in determining etiology of bacterial pneumonia.

4. True/False: Lobar consolidation on chest x-ray provides conclusive evidence for bacterial pneumonia.

5. Which factor does not appear to affect the etiology of pneumonia?
    a. Age
    b. Vaccination status
    c. Current antibiotic use
    d. Birth rank

6. The most common cause of bronchiolitis is:
    a. Respiratory syncytial virus
    b. Human Metapneumovirus
    c. Parainfluenza
    d. Adenovirus

7. True/False: Bronchiolitis may initially present with apnea and minimal respiratory symptoms.

8. Treatment of bronchiolitis should include all of the following except:
    a. Supplemental oxygen for infants with hypoxia.
    b. Intravenous fluids and close monitoring of nutritional status.
    c. Good handwashing.
    d. Antibiotics.

9. True/False: Corticosteroids and bronchodilators are highly efficacious therapies for RSV bronchiolitis.

Related x-rays

Pneumonia case presenting with abdominal pain: Yamamoto LG. Abdominal Pain with a Negative Abdominal Examination. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1994, volume 1, case 3. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v1c03.html

Staph pneumonia case: Yamamoto LG, Young LL. Tachypnea and Abdominal Pain. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1995, volume 2, case 5. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v2c05.html

Series of pediatric chest radiographs: Yamamoto LG. Test Your Skill In Reading Pediatric Chest Radiographs. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1995, volume 3, case 20. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v3c20.html

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Answers to questions

1.c. Overall, viruses cause the majority of pneumonias in children; however, the incidence of viral pneumonia decreases with age, becoming less common in older children and adolescents.

2.b

3.False
4.False. Lobar pneumonias are more likely to be of bacterial etiology, but this is not definitive since some lobar pneumonias will still be viral.
5.d
6.a
7.True
8.d
9.False

Chapter VI.12. Croup and Epiglottitis
Paul J. Eakin, MD

This is a 20 month old male who presents to the emergency department with a chief complaint of cough. Two days ago he developed rhinorrhea, fever, a hoarse cry and a progressively worsening, harsh, "barky," cough. Today he developed a "whistling" sound when he breathes, so his parents brought him to the emergency department. His past medical history is unremarkable. His 6 year old brother also has cold symptoms.

Exam: VS T 37.5, P 140, R 36, BP 90/64, oxygen saturation 96% in room air. He is alert, with good eye contact, in mild respiratory distress. He has a dry barking cough and a hoarse cry. He has some clear mucus rhinorrhea but no nasal flaring. His pharynx is slightly injected, but there is no enlargement or asymmetry. His heart is regular without murmurs. His lung exam shows good aeration and slight inspiratory stridor at rest. He has very slight subcostal retractions. No wheeze or rhonchi are noted. His abdomen is flat, soft, and non-tender. His extremities are warm and pink with good perfusion.

He is treated with nebulized racemic epinephrine and his coughing subsides and his stridor resolves. A lateral neck X-ray reveals no prevertebral soft tissue widening or evidence of epiglottitis. The subglottic region is mildly narrowed. He is treated with oral dexamethasone. He is discharged home after one hour of monitoring and his parents were instructed to treat him with humidified mist therapy.

Croup, which is derived from an Anglo-Saxon word meaning "to cry out", is a common respiratory illness in childhood. Croup is also known as laryngotracheitis and laryngotracheobronchitis (LTB). These terms will be used interchangeably in this chapter. The diagnosis describes a disease with some degree of laryngeal inflammation; resulting in hoarseness, a barking cough and varying degrees of respiratory distress over time. There are different etiologies encompassed in the diagnosis of croup, but the most common cause is viral, and this will be the focus of this chapter. The entity known as spasmodic croup is not easily distinguished from viral croup except that spasmodic croup has a greater tendency to recur. The treatment and evaluation are similar. When evaluating a child with croup, it is important to rule out epiglottitis, so this will be discussed as well.

Croup occurs most commonly between the ages of 1 and 6 years, with a peak incidence being around 18 months of age and the majority of cases below 3 years of age. It is more common in boys than girls. In temperate climates, it is most common during the late fall and winter, although cases can occur throughout the year.

Parainfluenza viruses are the most frequent cause of croup, accounting for more than 60% of cases. Less frequently associated with croup are influenza A and B, respiratory syncytial virus, adenovirus and measles. Bacterial superinfection can occur in cases of laryngotracheobronchitis and laryngotracheobronchopneumonitis.

Like most respiratory infections, the initial site of infection is thought to be the nasopharynx with subsequent spread to the larynx and trachea. The respiratory epithelium becomes diffusely inflamed and edematous, resulting in airway narrowing and stridor. Reduced mobility of the vocal cords results in a hoarse voice or cry.

Laryngotracheitis generally starts with several days of rhinorrhea, pharyngitis, low-grade fevers and a mild cough. Over the next 12 to 48 hours, a progressively worsening "barky" cough, hoarseness and inspiratory stridor are noted, secondary to some degree of upper airway obstruction and laryngeal inflammation. The speed of progression and degree of airway obstruction can vary widely. The onset is often rapid and typically in the early morning hours (e.g., 2:00 am). Croup symptoms appear to subside during the day (possibly because of positioning), only to recur the following night. Thus, a child with significant stridor presenting during daylight, may be more seriously affected. On examination, the child will be noted to have coryza, a hoarse voice, and varying degrees of pharyngeal inflammation, tachypnea, and stridor. More severe cases may involve nasal flaring, moderate tachypnea, retractions and cyanosis. Some children with croup may not be able to maintain adequate oral intake of fluids. Alveolar gas exchange is usually normal, with hypoxia seen only in severe cases. Symptoms of croup usually normalize over 3-7 days, although in severely affected children, this may take 7-14 days.

The diagnosis is usually made on clinical grounds. Laboratory studies add little to the diagnosis of croup if bacterial infection is not suspected. White blood cell counts may be elevated above 10,000 with a predominance of polymorphonuclear cells. White blood cell counts greater than 20,0000 with bandemia may suggest bacterial superinfection. Chest radiographs may show subglottic narrowing (in 50% of children with croup), but this can also be seen in normal patients. Lateral neck radiographs are often obtained, not as much to confirm the diagnosis of croup, but to rule out other causes of stridor such as soft tissue densities in the trachea, a retropharyngeal abscess and epiglottitis.

The most important diagnostic consideration is distinguishing acute epiglottitis from acute laryngotracheitis. Epiglottitis describes a bacterial infection of the epiglottis. It is most commonly caused by H. influenzae type B, and occasionally by S. pneumoniae and group A Streptococcus. The prevalence of epiglottitis has decreased markedly (almost non-existent) since the widespread use of H. influenzae B vaccine.

The peak incidence of epiglottitis is between the ages of 3 and 7 years, with cases described in infants and adults as well. It occurs throughout the year, but is more common in winter months. Children with epiglottitis do NOT have a "croupy" cough. They appear more toxic, stridorous, apprehensive, have higher fever (e.g., 40 degrees C, 104 degrees F) and will often be drooling. Patients will often be tachycardic and tachypneic. The child with epiglottitis may prefer to adopt a position of sitting up, leaning forward, with their chin pushed

forward and they may refuse to lie down. They will have a very inflamed, swollen epiglottis. Lateral neck radiographs may be helpful in making the diagnosis. X-rays are usually deferred if this diagnosis is suspected, owing to the critical clinical condition of the patient. The three characteristic findings on lateral neck X-ray are: a swollen epiglottis (thumb sign), thickened aryepiglottic folds and obliteration of the vallecula (pre-epiglottic space). Lab work is usually not done, but if done generally reveals elevated white blood cell counts with a left shift and blood cultures are positive in 80-90% of cases.

Other entities on the differential include bacterial laryngotracheobronchitis and laryngotracheobronchopneumonitis, which will have signs of lower respiratory involvement such as, wheezing and/or changes on chest x-ray. Often they will have hypoxia secondary to the lower airway disease. Retropharyngeal or peritonsillar abscess can cause upper airway obstruction, with soft tissue swelling evident on lateral neck x-ray (widening of the prevertebral soft tissue) or physical exam respectively. These children will often have high fever, drooling and be more toxic in appearance. Laryngitis can be seen in older children and adults, with a similar prodrome and cough, but lacking the inspiratory stridor. Foreign body aspiration should be considered in cases of sudden onset stridor without cough or fever. Acute angioneurotic edema, can cause acute swelling of the upper airway, but usually presents with external evidence of swelling of the face and neck. Laryngeal diphtheria (sometimes presents with a croup like syndrome known as membranous croup), although rare, should be considered and is another reason to assess the immunization record.

Once the diagnosis of croup is made, mist therapy, corticosteroids and epinephrine are the usual treatments. Since croup is chiefly viral in etiology, antibiotics play no role. Historically, mist therapy has been the mainstay of croup therapy, yet in small empiric trials, mist therapy has shown little benefit. Mist therapy (warm or cool) is thought to reduce the severity of croup by moistening the mucosa and reducing the viscosity of exudates, making coughing more productive. For patients with mild symptoms, mist therapy may be all that is required and can be provided at home.

For more severe cases, further intervention may be required. Oxygen should be provided to patients with hypoxemia. Racemic epinephrine, given by nebulizer, is thought to stimulate alpha-adrenergic receptors with subsequent constriction of arterioles and decreased laryngeal edema. Nebulized epinephrine may have marked effect to decrease inspiratory stridor and the work of breathing. Adverse effects include tachycardia and hypertension. The effects of this medication last less than two hours and children need to be monitored (not necessarily in the hospital) serially for the return of symptoms. Racemic epinephrine is a mixture of 50% biologically active epinephrine and 50% inactive epinephrine. The usual dose is 0.5cc of the 2.25% concentration diluted with 2cc of saline. 0.5cc of the 2.25% is equal to 11 mg of racemic epinephrine or 5.5 mg of plain epinephrine (0.5 cc of 2.25 gm/100cc = 11 mg). Thus, 5cc of 1:1000 epinephrine solution is pharmacologically similar and can also be used for inhalation therapy with a nebulizer if racemic epinephrine is not available.

Corticosteroids provide benefit for children with viral croup by reducing the severity and shortening the course of the symptoms. Dexamethasone is the most commonly used, with the dose being 0.6 mg/kg (maximum 10 mg) by mouth or intramuscularly. Clinical improvement from corticosteroids is usually not apparent until 6 hours after treatment. More recent studies have shown high dose nebulized budesonide to be as effective as dexamethasone, with more rapid onset of effect.

Endotracheal intubation is reserved for children with severe symptoms who do not respond to the previous therapies. This decision should be based on criteria such as hypercarbia, impending respiratory failure and changes in mental status.

If epiglottitis is suspected, the most serious complication is sudden airway obstruction. Because of this, airway management becomes the most important consideration. Visualization of the epiglottis should not be attempted, unless clinical suspicion is low or respiratory failure occurs. Assistance from a surgeon, intensivist, anesthesiologist, etc. (more than one is better), should be sought immediately since patients with epiglottitis may arrest at any time. Intubation is difficult so preparation should be made for intubation or tracheostomy. If the child is stable, it may be possible to start at intravenous line and obtain radiographic studies. Once the airway is secure, IV antibiotic therapy with either ceftriaxone or cefotaxime should be initiated. In the event of a respiratory arrest, mask ventilation with 100% FiO2 should be attempted using a two-person technique with one person ensuring a tight mask fit and the other squeezing the ventilation bag hard enough to drive air through the narrowed airway. Placing the patient prone (instead of the usual supine position) may improve ventilation by utilizing gravity to lift the epiglottitis off the larynx.

Most children with croup do extremely well and do not require hospitalization. Most children can be discharged from the emergency department after receiving dexamethasone and epinephrine therapy if they have no stridor at rest, normal color, aeration and level of consciousness and have been monitored for a period of time. 3-4 hours of observation is often recommended, but this is rarely followed in actual practice since most families are reluctant to remain in the emergency department during the early morning hours if their child is now sleeping comfortably.

Questions

1. Which of the following viruses are most commonly associated with viral croup?
    a. Adenovirus.
    b. Human papilloma virus
    c. Varicella virus
    d. Parainfluenza viruses
    e. RSV

2. True/False: An acutely ill child presents to the emergency department with the signs and symptoms of acute epiglottitis. The diagnosis should be confirmed with direct visualization of the epiglottis?

3. Which of the following is/are true?
    a. There is good evidence from randomized controlled trials that mist therapy is effective for the treatment of croup.
    b. Antibiotics are indicated in the treatment of croup.
    c. Nebulized albuterol is effective in the treatment of croup.
    d. Dexamethasone has been shown to be effective in the treatment of croup.

4. Which of the following is/are true?
   a. Croup affects more girls than boys.
   b. Croup shows no seasonal prevalence.
   c. Most cases occur in teenagers.
   d. It is a common respiratory infection in children.

5. True/False: Once a child with croup has been given corticosteroid treatment and racemic epinephrine, they may safely be discharged home after 20-30 minutes of monitoring.

Related x-rays

Comparison of croup, epiglottitis and retropharyngeal abscess: Boychuk RB. Drooling, Stridor, and a Barking Cough: Croup?? In: Yamamoto LG, Inaba AS, DiMauro R. Radiology Cases In Pediatric Emergency Medicine, 1994, volume 1, case 10. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v1c10.html

Series of lateral neck radiographs, some of which are retropharyngeal abscesses: Yamamoto LG. Test Your Skill In Reading Pediatric Lateral Necks. Yamamoto LG, Inaba AS, DiMauro R. Radiology Cases In Pediatric Emergency Medicine, 1995, volume 2, case 20. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v2c20.html

Membranous croup case: Yamamoto LG. Membranous Croup. In: Yamamoto LG, Inaba AS, DiMauro R. Radiology Cases In Pediatric Emergency Medicine, 1996, volume 5, case 20. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v5c20.html

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Answers to questions

1. d.

2. False. Routine airway visualization is stressful and may precipitate respiratory arrest. If epiglottitis is unlikely, then airway visualization appears to be safe. In the event of respiratory arrest, laryngoscopy will be necessary for tracheal intubation.

3. d is the best answer. c is also correct in that nebulized albuterol does have some efficacy in croup, but nebulized epinephrine is better.

4. d.

5. Most textbooks would suggest that this is false in that a longer observation period is generally recommended. However, most patients are low risk and can be discharged soon after dexamethasone and epinephrine are administered. Severe patients or those who do not respond as well should be observed for longer periods of time.

Chapter VI.13. Cellulitis
Leo U. Pascua, MD

A 2-year-old male presents to the emergency department with a chief complaint of left thigh swelling, fever, irritability, and unwillingness to stand upright for the last 2 days. He has been scratching at mosquito bites that he had gotten while weekend camping about 1 week ago.

Exam: VS T 39.5, P 110, R 26, BP 120/70. Growth parameters are normal for age. He is fussy, somewhat distractible, but clearly uncomfortable. He is continuously scratching at a left upper inner thigh lesion measuring 6 x 3 cm. The skin over the area is indurated, erythematous and tense, and tender. No fluctuance or wound drainage is noted. There is no joint involvement. Some tender lymph nodes are palpable in the left inguinal region.

He is prescribed cephalexin and anti-pyretics. In follow-up the next day, the erythematous region is slightly darker (a shift from red toward a shade of purple). Tiny blisters are also noted over the area. These changes are expected and treatment is continued. On follow-up day 2, the fever has resolved and the cellulitis appears to be clearly improving. His parents are instructed to finish the course of antibiotics. He is next seen in follow-up 7 days later, at which time, his cellulitis is resolved.

The basic response to infection is fever. The local, dermatological acute inflammatory reaction of cellulitis stems specifically from granulocytic infiltrations, hyperemia, and capillary leakage. This is the basis for the skin disruption inherent in cellulitis. The patient may guard the tender area. If the cellulitic area overlies a mobile area such as a joint, the patient may display resistance or anxiety with limb movement, either passive or active.

The specific visual characteristics (appearance) of the cellulitic region can provide important clues as to the organism(s) involved, with implications for treatment and prognosis. Clinical presentation, treatment, and prognosis differ depending on the causative organism and the location of the cellulitis. The remainder of this chapter will be stratified by these factors.

Group A strep cellulitis

Generally, cellulitis suggests the presence of a skin infection due to group A beta-hemolytic streptococci (GABHS, also known as Strep pyogenes). GABHS cellulitis is a painful, erythematous, indurated infection of the skin and subcutaneous tissues. It is classically described as large lesions, erythroderma in color (magenta), slightly raised at the border, with a small, central open skin lesion (frequently an insect bite). It is common for varicella lesions to become secondarily infection with GABHS. GABHS cellulitis may present with scarlet fever. Abscess formation beneath the cellulitis is very uncommon. GABHS is penicillin and cephalosporin sensitive.

Staph aureus cellulitis

Staph aureus is commonly cultured from impetigo lesions, albeit usually as a secondary pathogen, along with GABHS. Some of these lesions develop into cellulitis, which may be primarily caused by GABHS or alternatively, caused primarily by Staph aureus. Staph aureus cellulitis is typically smaller (than the larger GABHS cellulitis) and is frequently associated with an abscess or pustule. In many of these cases, the abscess is the major problem (i.e., incision and drainage is required), as opposed to the cellulitis which is relatively less of a problem.

H. flu type b cellulitis

H. influenzae type b (Hib) used to account for in 5-14% of the cellulitis cases in young children. More than 85% of children with H. influenzae type b cellulitis are 2 years of age or younger. Hib is a particularly virulent organism which is frequently associated with sepsis. A common location for Hib cellulitis was the periorbital and buccal region. Cellulitis is a complication of H. influenzae septic arthritis 10-30% of cases. Fortunately, there has been a substantial decline in the incidence of invasive infection caused by Hib with the practice of routine immunization of infants against this organism, to the point where Hib infection is almost non-existent. Hib is covered by high generation cephalosporins (e.g., ceftriaxone) and by broad spectrum oral drugs such as amoxicillin-clavulanate and cefuroxime.

Pasteurella/animal bite cellulitis

Cellulitis and lymphangitis typically appears 24-36 hours after mammalian bite injuries. The etiologies of infections following mammalian bites are polymicrobial and consist of mixed anaerobic and aerobic bacteria. In one study, an average of three different bacterial species was isolated from infected dog bites while a mean of five different species was recovered from infected human bites. Because of the numerous bacterial species in mammalian oral cavities and on the victim's skin, contamination of bite injuries is universal. Pasteurella multocida is sensitive to penicillins, but it is less sensitive to cephalosporins. Amoxicillin-clavulanate is generally used for animal bites to cover Pasteurella, staph aureus and anaerobes.

Orbital and periorbital cellulitis

Periorbital (preseptal) cellulitis involves inflammation of the lids and periorbital tissues without signs of true orbital involvement, such as proptosis or limitation of eye movement. It presents as a red and swollen infection limited to the superficial tissue layers anterior to the orbital septum. History usually yields an antecedent respiratory infection or bacteremia. Historically, H. influenzae type b was an important cause, and presented with fever, edema, tenderness, warmth of the lid, and, occasionally, purple discoloration (violaceous hue). However, streptococcal organisms are the most common cause of bacteremia associated with periorbital cellulitis in the post Hib-vaccinated era (9). S. pneumonia, Staphylococcus aureus, and group A beta-hemolytic streptococci cause clinically indistinguishable preseptal cellulitis (2). The latter two pathogens are more likely when fever is absent and with an interruption of the integument (e.g., an insect bite) (1).

Distinguishing periorbital from orbital cellulitis can be difficult. If proptosis, extraocular movement dysfunction, or visual deficits are clearly present, then orbital cellulitis is likely. However, in the absence of these findings, the diagnosis is unclear. In periorbital cellulitis, the lid swelling may be so severe, that it is not possible to tell if proptosis is present. A CT scan of the orbits will reliably distinguish periorbital from orbital cellulitis. Since the difference between the two can be important, a CT scan of the orbits has become routine in the evaluation of most patients with severe periorbital cellulitis and/or suspected orbital cellulitis.

Orbital cellulitis refers to a condition involving not only edema of the conjunctiva (chemosis), and inflammation and swelling of the eyelids, but also involvement of the tissues of the orbit, with subsequent proptosis (limitation of movement of the eye). In general, orbital

cellulitis may follow direct infection of the orbit from a wound, metastatic deposition of organisms during bacteremia, or direct extension or venous spread of infection from contiguous sites such as the lids, conjunctiva, globe, lacrimal gland, nasolacrimal sac, or paranasal sinuses. The most common cause of orbital cellulitis in children is paranasal sinusitis, with the most frequent pathogenic organisms being Haemophilus influenzae, Staphylococcus aureus, group A beta-hemolytic streptococci, and Streptococcus pneumonia. Orbital cellulitis must be recognized promptly and treated aggressively. Hospitalization and systemic antibiotic therapy are usually indicated. In some cases surgical intervention is necessary to drain infected sinuses, or a subperiosteal or orbital abscess. Intravenous treatment for 10 to 14 days is highly recommended, along with repeated eye exams (visual acuity, pupillary reactivity, extraocular movements, and visual fields) to evaluate possible progression of infection and/or involvement of the optic nerve (10). As a worst case scenario, orbital cellulitis can lead to the complication of brain abscess, especially in the frontal lobe.

Finally, orbital cellulitis is an infrequent presenting sign of retinoblastoma. The severe clinical implications of retinoblastoma (enucleation may be inevitable) warrants vigilance for a white pupillary reflex (leukocoria, the reflection of light off the white tumor), pseudohypopyon (tumor cells layered inferiorly in front of the iris caused by tumor seeding in the anterior chamber of the eye), and hyphema (blood layered in the anterior chamber) secondary to iris neovascularization or vitreous hemorrhage.

Erysipelas

Erysipelas is an acute, well-demarcated aggressive infection of the skin with lymphangitis involving the face (associated with pharyngitis) and extremities (wounds). The skin is erythematous and indurated. The advancing margins of the lesions have raised, firm borders. The skin lesion usually is associated with fever, vomiting, and irritability. In some cases, streptococci break through the lymphatic barrier (lymphangitis), and subcutaneous abscesses, bacteremia, and metastatic foci of infection are observed. Bacteremia and death have been associated with streptococcal cellulitis, and progression may be so rapid that there may be no response to treatment with penicillin. The popular press has termed severe cases of GABHS cellulitis (necrotizing fasciitis) as "flesh eating bacteria".

Lymphangitis

Lymphangitis is an inflammation of the lymphatics draining an area of infection (i.e., a cellulitis site). On exam, tender red streaks extend proximally from the infected site. S. aureus and group A strep are the most frequent pathogens. A history of impetigo is also suggestive of cellulitis, in that, cellulitis has been reported in approximately 10% of patients with nonbullous impetigo but rarely follows the bullous form. There is no correlation between the number of lesions and clinical involvement of the lymphatics or development of cellulitis in association with streptococcal impetigo. The history is consistent with pruritic lesions subject to frequent scratching and secondary infection (including insect bites, pediculosis and scabies). This is followed by the development of a vesicle or vesiculopustule with an erythematous base that erodes through the epidermis into the dermis to form an ulcer with elevated margins. A dry crust that contributes to the persistence of the infection obscures the ulcer. Lesions may be spread by autoinoculation, may be as large as 4 cm, and occur most frequently on the legs or pruritic areas within reach.

Risk of osteomyelitis and septic arthritis

Although the risk of osteomyelitis and septic arthritis is fairly rare unless a penetrating wound is present, the relationship between osteomyelitis and cellulitis deserves special attention, in that a progression to osteomyelitis from cellulitis mandates a far more aggressive and prolonged antibiotic course, not to mention possible orthopedic surgical debridement. Thus, when a diagnosis of cellulitis is made, the comorbid presence of osteomyelitis must also be strongly considered especially when corroborated by a history of a penetrating wound. At the very least, cellulitis accompanied by point tenderness or joint pain is highly suggestive of osteomyelitis. Attempts at diagnosis are complicated by the fact that cellulitis of structures in proximity to bone can mimic osteomyelitis.

To effectively discern cellulitis with possible underlying osteomyelitis, combining technetium bone scanning with other radionuclide scanning techniques or MRI scanning may be useful. In a three phase bone scan, focal increased uptake in the initial phase, with subsequent decline in the later phases (especially the bone phase), is suggestive of cellulitis without osteomyelitis. In osteomyelitis, localized uptake is seen in all three phases, especially in the bone phase.

If the history, physical exam, or radiological studies suggest deep cellulitis near a joint, the level of suspicion is raised with regard to an infection in the respective joint, not to mention osteomyelitis, synovitis, septic bursitis and pyomyositis in nearby muscles. Deep cellulitis is also consistent with psoas or retroperitoneal abscesses. Cellulitis overlying a joint can interfere with studies crucial to the diagnosis of septic arthritis. If a cellulitic area is traversed during arthrocentesis for a workup for septic arthritis, the results can be confounded if organisms are introduced into a previously sterile uninvolved joint.

Cellulitis and immunodeficiency

The presence of cellulitis in the face of concomitant immunodeficiency requires inpatient treatment. Deficient expression of leukocyte adherence glycoproteins can present as cellulitis or small (<1 cm) necrotic abscesses on any area of the body. In such cases, puncture wounds or skin surface trauma often precipitates cellulitis and abscess formation.

Defects in the normal host response may be reflected in study findings that are disproportionately severe when compared to relatively benign findings on the physical exam. For example, deep cellulitis may be quite impressive on a CT of a neutropenic patient who has only mild superficial swelling or erythema. Indeed, surface pus formation is unusual at sites of even severe cellulitis in such patients.

Cellulitis in children with burns illustrates not only the acute effects of interrupted skin and mucous membrane barriers, presence of necrotic tissue, long-term administration of antibiotics and prolonged intravenous or urinary catheterization, but also the concomitant abnormal immune response to infection, including neutrophil dysfunction. The resulting neutrophil chemotactic defect, combined with an associated hypogammaglobulinemia is a perfect scenario for cellulitis with Pseudomonas aeruginosa being the most common organism.

In the neonatal period, cellulitis can be a manifestation of invasive infection, as is bacteremia with a septic-like clinical picture, pneumonia, respiratory distress syndrome with shock, conjunctivitis, scalp abscess, or meningitis. Cellulitis may be the presenting sign of immunodeficiency in an infant. Cellulitis, delayed separation of the umbilical cord and gingivitis is consistent with an infant with leukocyte adhesion deficiency. Cellulitis of the labia majora, pyogenic skin infections, oral ulcerations, or abscesses has been the presenting manifestations of autoimmune neutropenia of infancy.

Cellulitis of the perirectal area, sites of iatrogenic puncture (central venous catheter insertion, venipuncture, lumbar puncture, and bone marrow biopsy), or abrasions is a setup for gram negative dissemination. In the context of vaginitis, beta-hemolytic streptococcus is

a common cause in prepubertal girls and may present with perianal cellulitis with local itching, pain, blood-streaked stools, erythema, and proctitis (3).

Rarely, cellulitis or skin discoloration overlying a fluctuant mass might be the presenting finding in tuberculosis of the superficial lymph nodes, often referred to as scrofula, the most common form of extrapulmonary tuberculosis in children. The tonsillar, anterior cervical, submandibular, and supraclavicular nodes become involved secondary to extension of a primary lesion of the upper lung fields or abdomen. The nodes usually enlarge gradually in the early stages of lymph node disease. They are firm (but not hard), discrete, and nontender. The nodes often feel fixed to underlying or overlying tissue. Disease is most often unilateral, but bilateral involvement may occur because of the crossover drainage patterns of lymphatic vessels in the chest and lower neck.

Cellulitis of the sublingual and submandibular spaces (Ludwig angina) tends to spread rapidly without lymph node involvement or abscess formation. It is an acute, life-threatening entity that may require tracheostomy in the event of respiratory obstruction.

Cellulitis of the auricle and external auditory canal is usually caused by S. pyogenes (GABHS) or occasionally by S. aureus. The skin is red, hot, and indurated, without a sharply defined border. Fever may be present with little or no exudate in the canal.

Cellulitis can be a complication of hidradenitis suppurativa, a chronic, inflammatory, suppurative disorder of the apocrine glands in the axillae or anogenital area, and occasionally, the scalp, posterior aspect of the ears, female breasts, and around the umbilicus. Cellulitis of the lateral nail fold can occur as spicules that have separated from the nail plate, penetrate the soft tissue. Predisposing factors include compression of the side of the toe from poorly fitting shoes, particularly if the great toes are abnormally long and the lateral nail folds are prominent, and improper cutting of the nail in a curvilinear manner rather than straight across. Oral antibiotics are necessary to treat cellulitis of the lateral nail fold.

Lab tests are generally not very helpful in cellulitis. A CBC might help to assess infection severity. A blood culture may be indicated if bacteremia or sepsis is suspected. A gram stain of a leading edge aspirate is done by injecting a small amount of non-bacteristatic saline into the leading edge of the cellulitis, then aspirating back the saline. Leading edge cultures have a low yield and they are usually not obtained. Since introduction of the Hib vaccine, the most common organisms are streptococci. In a series of 243 children admitted with cellulitis, Sadow and Chamberlain (1998) contend that, given a treatment threshold based on a band-to-neutrophil ratio of 0.20 on a CBC differential, routine cultures contribute little to the decision to treat (7). Most cases of early or mild cellulitis, especially those without fever, do not require laboratory testing. Empiric antibiotic treatment is successful in most instances.

Antibiotic treatment is targeted mainly against the usual pathogen, group A strep. Staph aureus is uncommon (unless an abscess is present), but difficult to exclude without a leading edge aspirate culture. GABHS is sensitive to penicillin and cephalosporins. Staph aureus used to be sensitive to anti-Staph aureus penicillins (cloxacillin, dicloxacillin, methicillin, oxacillin, nafcillin) and cephalosporins. However, currently, 25% of Staph aureus are resistant (i.e., methicillin and cephalosporin resistant). If GABHS is very likely, then utilizing a cephalosporin or penicillin is acceptable. However, if Staph aureus is suspected, then there is a 25% failure rate for cephalosporins and anti-Staph aureus penicillins. There is less Staph aureus resistance to clindamycin (also covers GABHS) and trimethoprim-sulfamethoxazole (does not cover GABHS as well). Thus, clindamycin is generally indicated if Staph aureus is suspected. Vancomycin and aminoglycosides are parenteral and can only be used for inpatient treatment of staph aureus. Erythromycin has been used in the past, but GABHS and Staph aureus have high resistance rates to erythromycin. If a satisfactory clinical response is not achieved within 7 days, a culture and sensitivity should be taken of a leading edge aspirate. If a resistant organism is detected, an appropriate antibiotic should be given for an additional 7 days.

Young children (<36 months of age) with pneumococcal facial lesions cellulitis are at risk for pneumococcal bacteremia, and usually present with fever and leukocytosis. With regard to prevention, a recent study noted that 96% of the pneumococcal serotypes causing facial cellulitis are included in the heptavalent-conjugated pneumococcal vaccine recently licensed in the United States (8).

Finally, aggressive attempts to restore skin integrity should be initiated. The skin should be gently moistened and cleansed. Impetiginous crusts should be softened with warm compresses and removed with an antibacterial soap. Application of an emollient provides lubrication and decreases discomfort. Topical antibiotics are unnecessary once systemic intervention is started.

Questions

1. A three-phase bone scan is being used to determine if osteomyelitis is coexisting in a cellulitis patient. Which finding would be consistent with the presence of osteomyelitis ?
   a. Focal increased uptake in the initial phase, with subsequent decline in the bone phase.
   b. Localized uptake in all three phases.

2. You are managing a serious pediatric burn victim who has developed cellulitis after repeated procedures for debridement of necrotic tissue. The patient has been on IV antibiotics and urinary catheterization since admission one month ago. Recent labs show hypogammaglobulinemia. The most likely pathogen is
   a. Pseudomonas aeruginosa
   b. Pasteurella multocida
   c. E. coli
   d. Herpesvirus
   e. Cryptosporidium

3. You are investigating a case of cellulitis secondary to a bite wound. The study shows seven different bacterial species isolates. The bite was most likely from:
   a. a human
   b. a cat
   c. a dog
   d. rat
   e. a pig

4. Which antibiotic class is NOT considered appropriate for outpatient treatment against cellulitis?
   a. Clindamycin
   b. Penicillin
   c. Cephalosporin
   d. Aminoglycoside

5. You have obtained a CT scan on a toxic-appearing patient, and the radiologist calls you to report a finding of an extensive deep cellulitis. A re-examination of the area shows only slight erythema superficial to the area of extensive deep cellulitis as seen on CT. A CBC of the patient is likely to show:
   a. neutropenia
   b. thrombocytopenia
   c. absolute lymphocytosis
   d. monocytosis
   e. increase red cell distribution width

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Answers to questions
1.b, 2.a, 3.a, 4.d, 5.a

Chapter VI.14. Meningitis
Raul Rudoy, MD, MPH

Case 1

A six month old male presents to the emergency department with a history of lethargy. He was seen 3 days ago with fever and URI symptoms, diagnosed with otitis media and treated with oral amoxicillin. This morning he had become irritable and was less active than usual. He has vomited three times and his urine output is noticeably decreased. He has no diarrhea.

Exam: VS T 40.0, P 90, R 30 (irregular), BP 120/90, weight 8kg. He is lethargic and arousable only to painful stimuli. His anterior fontanel is full and tense, and he has questionable neck rigidity. His TMs are red and bulging. His pupils are reactive, but his eyes do not focus well on his parents. His heart, lungs and abdomen are normal. His color and perfusion are good. He has no petechiae. He moves all his extremities weakly and his DTRs are hyperactive.

A CBC, blood culture and chemistry panel are drawn. An IV is started. Since an increased ICP (intracranial pressure) is suspected, a lumbar puncture (LP) is initially delayed and he is immediately given 500 mg of ceftriaxone IV. A stat CT scan of the brain is normal, so an LP is done and the CSF (cerebrospinal fluid) is visibly hazy. An infectious disease consultant is called to inquire about IV dexamethasone and vancomycin. Both are recommended and given. The CSF results return 1 hour later showing 450 WBCs, 95% segs, 5% monos, total protein 75, glucose 25 mg/dl. Gram stain of the CSF shows many WBCs with few gram positive cocci. He is admitted to the pediatric ICU.

The clinical presentation of this patient, with a very rapidly evolving febrile illness, changes in sensorium and evidence of increased intracranial pressure, is very compatible with a diagnosis of CNS (central nervous system) infection. Bacterial meningitis occurs more frequently between the ages of 2 months and two years. Acquisition of infected aerosolized particles, with initial colonization of the nasopharynx, is followed by subsequent replication in the regional lymph nodes, invasion, septicemia and CNS infection. The lack of anticapsular antibodies increases the risk of invasion. Rarely, the infection is due to spread from a contiguous focus such as the sinuses, the middle ear, or the mastoids. Bacterial meningitis secondary to otitis media is an uncommon phenomenon, but when it does occur, it is usually septicemic in origin, rather than due to direct extension.

Manifestations of bacterial meningitis are variable and depend upon the child's age and the duration of illness. In young infants, evidence of meningeal inflammation may be minimal and only irritability and poor feeding may be present. Body movements of infants with meningitis result in pain, accordingly a strong suspicion of CNS infection is aroused when the child does not wish to be handled but prefers to remain motionless. Such paradoxical irritability (which worsens when the child is carried, rocked or gently bounced), is highly suggestive of meningitis.

The older child will present with more clinical findings, such as nuchal rigidity, vomiting, lethargy and photophobia. Most cases of meningitis will be either of bacterial or viral etiology. Common bacterial causes in this age group include Streptococcus pneumonia

(pneumococcus) and Neisseria meningitidis (meningococcus). The advent of a very efficacious vaccine against H. influenzae type B, has resulted in an almost complete disappearance of meningitis due to this etiological agent. Prior to this vaccine, this was the most common cause of bacterial meningitis.

An LP is indicated in patients with clinical findings compatible with meningitis. Strong consideration should be given to delaying the LP in patients with clinical findings of increased intracranial pressure. However, antibiotic administration should not be delayed by this. Antibiotics must still be given immediately once bacterial meningitis is suspected. The patient in our case has evidence of increased intracranial pressure since he has decreased sensorium, a bulging tense fontanel, hyperactive reflexes and changes in the vital signs such as a decreased pulse rate, hypertension and irregular respirations (Cushing's triad). Accordingly, caution should be taken before performing the LP due to the possibility of precipitating herniation. A CT scan of the head is a very rapid and accurate means to confirm increased intracranial pressure and if present, measures such as the administration of mannitol and hyperventilation, after rapid sequence intubation, should be instituted before the LP is done. Analysis of the CSF is usually very useful in confirming the diagnosis of bacterial meningitis. Acute bacterial meningitis is characterized by an elevated CSF white count with a predominance of polymorphonuclear cells (neutrophils), a decreased CSF glucose level, an increased protein value and a positive gram strain and culture. Administration of oral antibiotics prior to the LP, do not greatly modify the LP results, except for a slight decrease in the rate of identifying the organism on gram strain and cultures.

The treatment of meningitis is directed at reducing the damage produced by the inflammatory response by maintaining adequate cerebral perfusion with the use of adequate amounts of intravenous fluids and agents that reduce intracranial pressure and by treating the infection. The use of a third generation cephalosporin such as cefotaxime (50 mg/kg dose every 6 hours) or ceftriaxone (100 mg/kg day in one dose) provides coverage for most of the agents responsible (pneumococcus, meningococcus, H. influenzae type B) for meningitis except for penicillin-resistant pneumococcus which require the addition of vancomycin. Antibiotics used to treat meningitis must reliably penetrate the blood brain barrier in addition to reliably cover the organisms involved. The duration of treatment is dictated mostly by the clinical course but usually is 5 to 7 days for meningococcal infections and 10 days for infections due to pneumococcus. Neonatal meningitis has a different group of etiologic bacteria and antibiotics which are covered in the chapter on neonatal sepsis.

The survival of patients with bacterial meningitis has improved but it still remains a disease with high morbidity. Approximately half of those with S. pneumoniae and 15 percent of those with H. influenzae meningitis will develop neurological sequela. Cerebral infarction occurs in 5 to 20 percent of the patients as a result of localized inadequate perfusion due to local thrombosis, arteriolar vasculitis and phlebitis secondary to the inflammatory response. Sensorineural hearing loss is the most common sequela occurring in approximately 15 percent of cases. The hearing loss is usually severe, bilateral and permanent, and it occurs during the first few days of the infection. Penetration of bacteria through the internal auditory canal results in inflammation and destruction of the auditory nerve. Reduction in the incidence of hearing loss was reported with the use of corticosteroids (dexamethasone) for cases of H. influenzae meningitis, but proof supporting the benefit of corticosteroids with other causes of bacterial meningitis is not as evident. The use of corticosteroids is currently controversial due to the decrease in cases of H. influenzae meningitis (due to routine H. influenzae vaccine) and the fact that most cases of bacterial meningitis are now caused by pneumococcus and meningococcus, for which the benefit of corticosteroids is less proven.

Primary prevention of meningitis is accomplished by the administration of H. influenzae type B and S. pneumoniae vaccines to infants. Meningococcal vaccine is also available, but it is not routinely recommended, except adolescents and adults residing in dormitories or military barracks. Secondary prevention, with antibiotics such as rifampin is recommended for close contacts of patients with invasive H. influenzae type B and N. meningitis disease (but not for pneumococcal meningitis).

Case 2

A three year old female presents to the emergency department with a two day history of headache, nausea, vomiting and fever. She was seen by a physician two days ago who diagnosed otitis media and prescribed amoxicillin. She has taken six doses. Her immunizations are up to date. She is conscious, alert and complains of pain over the neck area. On examination she has pain on flexion of the neck. An LP showed 453 WBCs with 75% neutrophils and a glucose of 50 mg% (blood glucose 90 mg%) and a protein value of 55 mg%. A gram strain is negative for bacteria. Her headache improves and she appears less ill following the LP. She is admitted to the hospital with the diagnosis of viral meningitis. A repeat LP done 20 hours after the initial LP, shows 315 WBCs with 83% lymphocytes and a glucose value of 75 mg%, blood glucose of 89 mg%, and protein of 30 mg%. She is largely asymptomatic following the second LP. CSF cultures remain negative. A CSF PCR for enterovirus is positive.

Aseptic meningitis is characterized by lymphocytic/monocytic predominance of the CSF differential. The CSF protein is not as high and the glucose is not as low, compared to bacterial meningitis. Aseptic meningitis is almost always due to viral etiologies; however the rare case of tuberculous and fungal meningitis will present as an aseptic meningitis as well. Patients with viral meningitis can have all of the signs and symptoms of patients with bacterial meningitis; however, their findings are less severe. The classic patient with bacterial meningitis is toxic in appearance, irritable, and/or lethargic, possibly with other signs of sepsis. The typical patient with viral meningitis is alert and cooperative, but uncomfortable and mildly ill. Young infants are the most difficult to assess. Older cooperative children who can speak and express their symptoms are easier to evaluate. A lumbar puncture has two advantages in cases of viral meningitis in that it will usually ascertain a firm diagnosis and it will usually provide some degree of headache relief.

CSF neutrophil predominance can be initially seen in up to two thirds of cases of meningitis due to enterovirus and a slight decrease in the CSF blood glucose ratio occurs in one fourth of pediatric enteroviral meningitis. The low protein value and the relative low WBC are also indicative of a viral etiology. Enteroviruses are the leading cause of aseptic meningitis and account for 90 percent of all cases in which a pathogen is identified. Infants and children are most commonly affected and the prognosis is generally excellent. A CSF PCR for enterovirus is highly accurate in making an etiological diagnosis and will be positive in the great majority of cases. The repeated LP done 12 to 24 hours after the first will show a rapid shift in the CSF differential count from neutrophils to mononuclear predominance.

Questions

1. A three year old male presents with a bad headache, nausea, photophobia and fever (temp 38 degrees). His immunizations are up to date. He is not toxic in appearance. He is alert and cooperative. He has mild photophobia and mild nuchal discomfort without rigidity. He can speak and ambulate normally. The remainder of his exam is unremarkable. If this patient has meningitis, does he/she have bacterial or viral meningitis? What factors suggest one or the other?

2. An LP is done on the patient in question #1. The results show the following: 3 RBCs, 200 WBCs, 70% segs, 10% lymphs, 20 % monos, total protein 45, glucose 50. Gram stain of the CSF shows many WBCs and no organisms seen. Is this CSF analysis consistent with bacterial or viral meningitis? Which factors suggest one or the other?

3. What are the three most common bacteria that cause meningitis and what antibiotic covers them with close to 100% certainty?

4. Match the CSF results with the diagnosis (normal CSF, viral meningitis, bacterial meningitis). Validate your answer. Assume that the patient is 6 months old.

CSF	CSF 1	CSF 2	CSF 3	CSF 4
White cells	1243	5	190	250
%Neutrophils	94%	1%	60%	86%
CSF Glucose	23	65	50	47
Blood Glucose	78	85	87	90
Protein	62	21	48	49

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Answers to questions

1. This is most likely a viral meningitis. He is older, so his risk of bacterial meningitis is lower. He has been fully immunized, which presumably means that he has had H. influenzae, type B vaccine. He has probably had pneumococcal vaccine, but this can't be automatically assumed. He is alert, ambulatory, and not toxic in appearance, which all suggest that he does not have an overwhelming infection such as bacterial meningitis.

2. This is most consistent with viral meningitis. Although he has a high percentage of segs, this is still consistent with early viral meningitis. Cases of bacterial meningitis which have not been pre-treated with antibiotics almost always have more than 90% segs. The gram stain does not show any organisms which makes bacterial meningitis less likely. This laboratory analysis of his CSF suggesting viral meningitis, is consistent with his clinical appearance which also suggests viral meningitis (see the answer to #1 above).

3. Pneumococcus, meningococcus and Haemophilus influenzae type B. Pneumococcus is usually sensitive to penicillins and cephalosporins, but some resistance has emerged so vancomycin should be given in addition to cefotaxime or ceftriaxone. Meningococcus is sensitive to penicillin so cefotaxime or ceftriaxone provides sufficient coverage. H. influenzae type B is sensitive to cefotaxime and ceftriaxone, but this organism is not a common cause of bacterial meningitis due to widespread immunization against this organism.

4. CSF 1 shows bacterial meningitis. The increased number of cells in the CSF with a predominant number of neutrophils makes this a strong likelihood possibility. In addition, he also has a very low glucose CSF level (CSF, blood glucose ratio of 25%) and an increased protein value sometimes. Cases of early viral meningitis can present with an increased number of cells and neutrophils but usually the CSF glucose is normal or not lower than 40% of the blood CSF value.

CSF 2 is normal. The normal number of WBCs in the CSF depends upon the age of the patient. The younger and more immature the infant is, the higher the value is. CSF glucose value depends upon the value of glucose in the blood and upon the integrity of the blood brain barrier. In patients with normal meninges the CSF value is usually about 75% of the blood level. When the meninges become inflamed, the active transport of glucose across the blood brain barrier becomes altered and the ratio drops proportionately to the degree of inflammation. Most viral meningitis produce less changes than bacterial meningitis accordingly CSF glucose values are lower in bacterial meningitis.

CSF 3 shows viral meningitis. Most cases of viral meningitis will present with a moderate increase in the number of white cells and a percentage of neutrophils not higher than 60-70%.

CSF 4 is inconclusive. The high percentage of neutrophils indicates that bacterial meningitis is possible. It would be wise to administer antibiotics until more information can be obtained. The gram stain result will be helpful. If it is positive for organisms, then this indicates bacterial meningitis. If the gram stain is negative, bacterial meningitis still cannot be totally ruled out. The child's clinical condition is not part of this table, but in reality, a child who is alert, active and playful is more likely to have viral meningitis, as opposed to a lethargic, toxic child who is more likely to have bacterial meningitis. This will probably turn out to be a case of viral meningitis despite the high percentage of neutrophils, since an early viral meningitis will often have high neutrophil percentages. A repeat LP 12 to 24 hours from the first LP will be helpful. A repeat LP which demonstrates a clear shift toward mononuclear cells, is consistent with viral meningitis, while no shift, or only a slight shift would suggest bacterial meningitis. Culture of the CSF will be most definitive if it is positive, but this result will not be available for at least 24 hours.

Chapter VI.15. Encephalitis
Jonathan K. Marr, MD

This is a healthy 11 year old male who is taken to his PMD for persistent headaches for the last 4 days despite treatment with acetaminophen and ibuprofen at home. He has had intermittent emesis and tactile fever for the last three days and has had minimal oral intake over the last 36 hours. There was no history of trauma, but he has had recent URI symptoms 2 weeks ago. After evaluation by his PMD, he is sent to the lab for tests when his mother notes that he is more sleepy and unresponsive. While going to the lab for tests, he develops shaking movements on the left side of his body. 911 is called and he is taken to an emergency department via ambulance. An IV is started and he is given diazepam IV which promptly stops the seizure activity.

VS: T 38.6, P 136, R 15 (shallow), BP 108/65, oxygen saturation 100% with mask. Wt 40kg. He is unresponsive to voice commands and he has shallow respirations. His head shows no signs of trauma. His pupils are equal at 3 mm and reactive to light. No papilledema on funduscopic exam is noted. His oral mucosa is moist with no oral lesions. His neck is supple without adenopathy. Heart is regular. Lungs are clear with shallow aeration. His abdomen is normal. His pulses, color and perfusion are good. He has several bug bites on his extremities without signs of cellulitis, petechiae, or bruises. He has increased tone to the left side of his body and brisk reflexes L>R. He is nonresponsive to voice commands, but he withdraws to pain. He exhibits no purposeful movements or signs of posturing. His corneal reflex, oculocephalic, and oculovestibular responses intact.

Encephalitis is suspected. He is given IV loading doses of fosphenytoin, acyclovir, and ceftriaxone. Lab studies show a normal CBC, chemistry, and liver function studies. Urine and serum toxicology screens are pending. A head CT without contrast shows no evidence of intracranial mass, ventriculomegaly, or intracranial bleed. A lumbar puncture is done. Opening pressure is 10 cm H20. CSF analysis shows 58 WBC (65% segs, 26% lymphs, 9% mono), protein 95, glucose 40, 4th tube on hold. Gram stain of the CSF shows few WBCs, but no organisms seen.

He is transferred to the PICU for further management.

Encephalitis is defined as an acute infection with focal or diffuse inflammation of brain parenchyma usually from viral etiologies, but it may also be associated with bacterial, fungal, protozoan, and autoimmune processes. Most often, encephalitis is an unusual complication of common systemic infections. Clinical manifestations reflect damage to neural cells that impair neural cell function through immune responses (1). The probability and severity of encephalitis can often be determined by: seasonality, age of infected groups, geographic distribution, availability of vaccines, animal or insect vector involvement, and immune-competency of the host.

The estimated incidence of viral encephalitis in the United States according to the Center for Disease Control (CDC) is 20,000 cases per year (5). It is an infrequent disease, occurring predominantly in children (16 per 100,000), elderly, and immunocompromised hosts (1). The incidence is highest in the second year of life (17 per 100,000 child years) and declines to 1 per 100,000 at age 15 (2). Overall mortality is 3 to 4% and morbidity is 7 to 10%. Endemic causes of encephalitis in the United States include herpes simplex virus (HSV), rabies virus, and La Cross virus. HSV is the most common cause of severe encephalitis in children and accounts for approximately 10% of all cases of encephalitis in the United States (2,4,5). Neonatal HSV-2 encephalitis with treatment, has a mortality of 14% (compared to 85% without treatment) and severe neurological dysfunction is found in 50 to 70% of affected individuals (2). HSV-1 encephalitis in older children represents the commonest cause of nonepidemic fatal viral encephalitis with a mortality of 30 to 50% and major neurological sequelae in 40 to 50% (2,6). Rabies virus infection accounts for several thousand deaths per year in Asian countries. In contrast, rabies virus is a rare cause of death or encephalitis in the United States due to the mandatory vaccination program of domestic canines. There are less than 5 indigenous cases of human rabies per year in the United States. One article, however, has suggested that the incidence in the United States may be increasing because of the changing epidemiology of infection in animal populations (5).

Arthropod-borne viruses (arboviruses) are agents of several virus families that can replicate in both invertebrate and vertebrate cells. Replication and infection of the hematophagous host must occur prior to injection of the vertebrate host. Over 400 arboviruses produce four major clinical syndromes associated with human arboviral infections: 1) encephalitis, 2) yellow fever, 3) hemorrhagic fevers, and 4) undifferentiated tropical fevers (6). La Cross virus is the most common cause of endemic arboviral encephalitis. St. Louis encephalitis is geographically the most widespread arbovirus in the United States and the commonest cause of epidemic viral encephalitis. The CDC receives reports of 200-500 cases of arboviral encephalitis per year. Encephalitis due to La Cross virus characteristically affects males (male:female ratio 2:1) 5-15 years of age in Wisconsin and Ohio, occurs from June to early October, and has less than 1% mortality (2,4,5). St. Louis encephalitis, in contrast, causes large urban epidemics among the elderly and occurs more frequently in the lower socioeconomic groups in the Midwestern and southeastern United States in late August and September following heavy spring rains and summer droughts. The virus is more common in urban environments where there is stagnant water with high organic content, particularly poorly draining sewage (6). Mortality ranges from 3 to 20%. Worldwide, Japanese encephalitis is the most common cause of arthropod-borne encephalitis with over 50,000 cases reported per year in China, Southeast Asia, and India (5). During epidemics, mortality ranges from 20 to 40%, with death usually occurring in the first week of illness (4). Eastern Equine encephalitis has peak activity from August to September and is geographically located along the eastern coast from Massachusetts to Florida. Compared to other arboviral encephalitides, Eastern Equine encephalitis symptoms are more severe and mortality is greatest at 50 to 75%. Mosquito-borne viruses peak in late summer in temperate regions, whereas tick-borne diseases occur in spring and early summer.

Post-infectious encephalomyelitis is an acute, inflammatory, demyelinating disease affecting multiple levels of the central nervous system (brain, optic nerves, and spinal cord) and occurs after a respiratory tract infection, viral exanthem, or an immunization. Synonymous names include: acute disseminated encephalomyelitis, acute demyelinating encephalomyelitis, and postviral encephalomyelitis. Occurrence is rare before 1 year of age, and it accounts for 10-15% of acute encephalitis cases in the United States (1) with peak incidence at 5 to 6 years of age. Historically, postinfectious encephalomyelitis was a complication of vaccinia immunization and measles virus infections; however, the discontinuation of vaccination against smallpox has eliminated the former, and immunization against measles has greatly reduced the later. Currently, post-infectious encephalitis in the United States is most commonly associated with varicella-zoster virus and influenza virus (5); although true postinfectious encephalomyelitis as a complication of varicella or influenza are rare (6). Other infections associated with postinfectious encephalomyelitis include: rubella, Mycoplasma pneumoniae, EBV, mumps, and human herpes virus 6 (HHV-6) (2,6). Worldwide there are over 100,000 cases that occur secondary to measles infection (5). Encephalitis from measles in the United States, in contrast, occurs in one per thousand cases (2). The incidence of post-infectious encephalitis has declined precipitously in countries following implementation of vaccination against measles, mumps, and rubella.

Viral encephalitis can be transmitted in one of two ways: via animal or insect vectors that transmit viruses maintained in environmental reservoirs or by human transmission via direct contact with human blood or body fluids. Epidemiologically, this is important since environmentally derived viral pathogens display relatively uniform epidemiologic characteristics. Furthermore, human disease correlates with the life cycle of the vector (spring and summer) and exhibits a geographic distribution that parallels with the habitat of the vector. In contrast, viruses transmitted human-to-human display few seasonal, temporal, or geographic predilections.

Central nervous system (CNS) infection depends, in large measure, on the magnitude and duration of the viremia, which reflect, in turn, the efficiency of the viral replication at extraneural locations and the ability to evade host defense mechanisms. The spectrum and severity of neurological signs and symptoms depends on neurovirulence (the capacity to cause disease within the CNS) and neurotropism (the propensity to infect specific cell groups of the CNS) (1). In human disease, the difference in neurovirulence between viruses is striking. For example, mumps is very highly neuroinvasive, but its neurotropism appears limited to ependymal cells, which may account for the low level of neurovirulence. In contrast, herpes simplex virus is thought to be relatively nonneuroinvasive, but when the CNS is infected, neurons, glial cells, pia-arachnoid cells, and endothelial cells are all affected and, without appropriate treatment, a 70% mortality bespeaks a very high degree of neurovirulence (6).

Infectious encephalitis is the result of direct invasion of any cell type in the brain and gains entry via hematogenous or neuronal routes. Most viral CNS infections are acquired hematogenously and current evidence indicates that most viruses grow at some extraneural site (usually the reticuloendothelial system), establish a viremia, and cross from blood to brain or cerebrospinal fluid by varied pathways: 1) via cerebral capillaries, 2) transfer via pinocytotic vesicles across capillary endothelial cells, and 3) via the fenestrated vascular endothelial cells of the choroid plexus (6). Hematogenous spread is exemplified by neonatal (HSV-2) herpes encephalitis and arthropod-born viral disease. Transmission of virus into the brain through neural pathways include 1) bidirectional axonal transport, and 2) cell-to-cell infection (6). Rabies, HSV-1, and varicella-zoster virus exemplify neural transmission of viruses into the CNS.

Post-infectious encephalitis is likely an autoimmune cell-mediated immune process characterized by perivenulitis and contiguous demyelination (1) caused by derangement and dysregulation of the immune system following either respiratory or intestinal tract infections. A viral infection may activate myelin-reactive T-cells that migrate to the CNS. These cells may activate other mediators of inflammation, including inflammatory cytokines that trigger demyelination.

Clinical manifestations of encephalitis in the neonatal period are often nonspecific and include: fever, poor feeding, irritability, lethargy, and sepsis. Apnea, focal or generalized seizures, paralysis, or coma may appear with progressive neonatal herpes simplex encephalitis. The mean age at onset of neonatal HSV encephalitis is 11-14 days after birth. HSV-2 is usually the etiological agent in 3/4 of cases and is acquired either by intrapartum contact of the fetus with maternal genital secretions (85-95%) or in utero (5-15%). Primary maternal genital HSV infection poses a much greater risk to the fetus than recurrent genital infection, since the initial viremia and the lack of protective antibodies against HSV are more likely to result in disease. The risk of transmission from mother to fetus is 30-50% with maternal primary infection, as compared with <3% with recurrent infection (4). Overall, 50% of infants with neonatal HSV infection will have encephalitis as a component of their disease (1,2). The presence of microcephaly, hydranencephaly, microphthalmia, chorioretinitis, cataracts, intracranial calcifications, intrauterine growth retardation, and vesicular rash are characteristic of in utero acquisition of HSV-2. This latter presentation is due to congenital infection (hematogenous exposure during early gestation usually from primary maternal HSV), as opposed to the former presentation which is a perinatal infection acquired close to the time of delivery.

In older children, the clinical manifestations of the inflammatory response are initially subtle and diverse. Specific neurological findings vary according to which areas of brain parenchyma are affected and also the degree of increased intracranial pressure. Some features of acute encephalitis are similar to those found in aseptic meningitis and include headache, stiff neck, photophobia, fever, vomiting, and irritability; however, the hallmark of disease is alteration of higher cerebral function, characterized by change in level of consciousness, psychiatric and behavioral abnormalities, and/or seizure activity. Predominant cortical involvement may lead to disorientation and confusion. Basal ganglia involvement may lead to movement disorders and brainstem involvement may lead to cranial nerve dysfunction. Occasionally, spinal cord involvement (myelitis) may accompany the encephalitis with findings of flaccid paraplegia and abnormalities of the deep tendon reflexes.

HSV encephalitis in the older child may represent primary infection, reinfection, or reactivation of latent infection. Most cases (about 70%) are the due to reactivation in the olfactory bulb or trigeminal ganglia and resultant spread into the CNS. Encephalitis may begin suddenly or after a brief influenza-like prodrome. Initial symptoms include: fever (always present) with headache, vomiting, malaise, behavioral changes, and speech difficulties. Consciousness decreases with progression and focal seizures are prominent (40%). Focal neurological signs, such as hemiparesis, dysphagia, or visual field defects develop and likely reflect selective involvement of the temporal or frontal lobes. The clinical course of HSV encephalitis can be rapidly progressive, with refractory seizures (status epilepticus), coma, increased ICP, and death within 2 weeks. The clinical course, however, may become more chronic and result in seizures, memory loss, and behavioral disturbances. Pathological studies have shown localized inflammation, necrosis, and inclusion bodies, with strikingly unilateral frontal-temporal localization (6). This pathologic finding suggests that the virus is spread from cell to cell along the base of the brain within the middle and anterior fossae.

Of the nearly 100 known herpesviruses of non-humans, eight human herpesviruses (HSV 1 & 2, cytomegalovirus (CMV), varicella-zoster virus, Epstein-Barr virus (EBV), and human herpesvirus 6, 7, & 8) are prevalent in all human populations and seven are capable of persisting for life. All eight human herpesvirus infections are associated with acute encephalitis. Acquired cytomegalovirus (CMV) infections in immunocompetent hosts are rarely associated with neurological complications, but when they occur, the encephalitis is often mild, and self-limited. Encephalitis from varicella-zoster virus usually appears 3-7 days after onset of the rash and consists of headache, fever, seizures, paralysis, and coma (1). Epstein-Barr virus (EBV) encephalitis accounts for 5% of cases of acute encephalitis and is the most common infectious agent mimicking HSV encephalitis (1). Clinical manifestations of acute encephalitis include: fever, headache, altered consciousness, and seizures, including status epilepticus. EBV infection also produces the "Alice-in-Wonderland" syndrome characterized by bizarre personality changes and perceptual misinterpretation (metamorphosia of size, shape, and or distance) (1). Human herpes virus type 6 and 7 (HHV-6 and HHV-7) causes roseola (exanthem subitum) in young children and account for a substantial proportion of febrile seizures of childhood. HHV-6 or HHV-7 have been linked with acute encephalopathy and encephalitis in young children with symptomatic infections having high fevers and seizures that are usually generalized. Hemiparesis (transient or permanent) and coma may be additional clinical features (1).

Encephalitis from arboviruses in pediatrics are usually the result of La Cross virus, a California serogroup virus, which is transmitted from the vector, Aedes triseriatus, a forest dwelling mosquito residing in wooded areas of the midwestern and mid-Atlantic United States. The virus is maintained in the wild through a mosquito and small woodland mammal (chipmunks, rabbits, and squirrels) cycle. Unlike eastern, western, and St. Louis encephalitis, the transmission cycles do not involve an avian reservoir (6). There are

approximately 100 cases per year in children 5 to 11 years of age. The clinical course is mild and characterized by headache, fever, malaise, abdominal pain, and vomiting for 3 to 7 days after exposed to the virus. Lethargy, behavioral changes, and/or brief seizures follow with clinical improvement over a 7 to 8 day period. Focal neurological signs are present in 16 to 25%, suggesting a diagnosis of HSV encephalitis and may necessitate initiation of treatment. Fifty percent develop seizures and 10 to 15% of children develop status epilepticus. Mortality is less than 1% (4).

St. Louis encephalitis virus is endemic in the midwestern United States and is maintained in a mosquito-bird cycle involving Culex tarsalis mosquitoes, pigeons, sparrows, and doves. Most infections are asymptomatic; however, two-thirds of symptomatic infections present with encephalitis. Children have a biphasic illness first with low-grade fever, diarrhea, vomiting, and malaise followed by the rapid onset of headache, vomiting, fever (as high as 41 C), neck stiffness, lethargy, and/or agitation. Tremors may be present, but focal neurological findings are infrequent. Clinical improvement begins within 7 to 10 days of disease onset. Syndrome of inappropriate antidiuretic hormone (SIADH) with hyponatremia, dysuria with pyuria, opsoclonus, myoclonus, and oculomotor paralysis are unique clinical features of this form of encephalitis (6). Mortality ranges from 8 to 20% with most deaths within the first 2 weeks. Approximately 10% of survivors experience sequelae of memory loss, chronic fatigue, sleeplessness, headaches, and occasionally seizures or motor deficits.

Japanese encephalitis causes more neurologic morbidity and mortality than all of the other arboviruses combined and is the most common arthropod-borne encephalitis worldwide with over 50,000 cases per year in Asia. The virus is maintained in a bird-vertebrate cycle involving Culex tritaeniorhynchus mosquitoes that breed in rice fields, domestic pigs, young water buffalo, herons and other wading birds (1,6). Children affected are usually under 15 years of age and have an abrupt, fulminant illness with rapid depression of consciousness, fever, vomiting, increased muscle tone, convulsions, and coma. The virus may infect brain stem nuclei, leading to acute respiratory failure and death. Infection of the basal ganglia and thalamus presents as tremors during the acute disease and result in parkinsonian mask-like facies, rigidity, tremor, and dystonia in survivors (4). Decorticate and decerebrate posturing are notorious clinical features in Japanese encephalitis. Mortality ranges from 25 to 40% with the majority of survivors having mental retardation, seizures, motor deficits, or subtle behavioral and intellectual abnormalities. Infection may be prevented with an inactivated Japanese encephalitis virus vaccine prepared by infected mouse brains.

Eastern equine encephalitis virus has the lowest incidence in North America, but has the highest mortality rate. Geographically, the eastern encephalitis virus is found in the eastern half of the United States primarily along the freshwater marshes of the Atlantic and Gulf coasts from Massachusetts to Florida. Peak activity occurs in August and September. The rarity of human disease is explained by the cycle of the virus that is usually transmitted between marsh birds and Culiseta melanura mosquitoes, which do not feed on large vertebrates. Only with alterations in the conditions of the marshes, changes in rainfall, different bird populations, and variations in mosquito breeding, can the virus spill over into other mosquito vectors that feed on mammals. Human outbreaks usually are heralded by deaths among horses and pheasants (4,6). Although the disorder usually begins with abrupt onset high fever, lethargy, vomiting, and convulsions, some have a prodromal phase of fever, headache, malaise, and myalgia. Signs are usually diffuse, but some may have focal findings suggesting focal encephalitides, such as HSV. Mortality ranges from 50 to 75% with neurological sequelae of mental retardation, seizures, spastic paralysis, and behavioral abnormalities (1). The Asian Tiger mosquito (Aedes albopictus) was imported into Houston, Texas in 1985 in a shipment of used tires. In 1991, Eastern encephalitis virus was recovered in the Asian Tiger mosquito and has raised major concerns since the mosquito is an aggressive biter of humans which thrives in suburban and forest habitats and could become a treacherous host for the eastern encephalitis virus (6).

The differential diagnosis for acute encephalitis includes: bacterial meningitis, Rocky Mountain spotted fever, brain abscesses, drug intoxication, lead encephalopathy, Reye's syndrome, hepatic coma, uremia, organic acidemias, amino acidemias, urea cycle defects, intracranial neoplasms, systemic lupus erythematosus, cerebrovascular accidents, pseudotumor cerebri, trauma, and post-infectious encephalopathies. The presence of fever is helpful in distinguishing encephalitis from encephalopathies due to toxins or inborn errors of metabolism.

Evaluation of an infant, child, or adolescent with signs of neurological dysfunction with or without fever requires a thorough neurodiagnostic assessment that may include: cerebrospinal fluid (CSF) examination, electroencephalogram (EEG), and imaging studies of the brain and/or spinal cord. The sequence of these studies will depend on severity of condition and concerns regarding possibility of CNS mass lesion, presence of increased intracranial pressure, or other acute neurological conditions requiring specific intervention.

In general, there is little correlation of CSF abnormalities with clinical or histologic severity of encephalitis. The CSF is usually clear and colorless, but may be xanthochromic when blood has been in the CSF for some time. The CSF cell count and protein are frequently normal or slightly elevated, and the glucose concentration remains normal. In the early phase of viral infection, there is often a mixed pleocytosis with both polymorphonuclear (PMN) and mononuclear cells that typically shifts to a lymphocytic pleocytosis over time (1,2). Subsequent lumbar punctures can be helpful in demonstrating pleocytosis. Eastern equine encephalitis has CSF parameters which appear more "bacterial" than "viral," with a predominance of PMN pleocytosis that persists throughout the illness (1,2). Although HSV-1 typically produces lytic infection of neuronal cells and causes hemorrhagic necrosis of the brain (1), the presence of red blood cells in the CSF is a late and inconsistent indicator of HSV encephalitis. Consideration must also be given to subarachnoid hemorrhage from occult trauma or vascular malformation. Vasculitis or tissue necrosis elicits CSF leukocytosis with increased PMN cells and also causes extravasation of red blood cells into CSF (2).

Cell culture provides direct evidence of infection by detecting viral pathogens from CSF, blood, or other body fluids. Viruses that can be detected via this diagnostic approach include herpesvirus, enterovirus, adenovirus, HIV, and rabies. Yields typically are very poor: viral CSF cultures are positive in less than 30% of neonatal HSV encephalitis or disseminated disease (5). Additionally, CSF viral cultures for HSV-1 are almost always negative (4) for older children with HSV encephalitis (2). As for the arboviruses, La Cross virus, St. Louis, and eastern equine encephalitis virus are not typically isolated.

Polymerase chain reaction (PCR) is an inexpensive, rapid, molecular genetic assay that detects specific organism DNA sequences and provides confirmatory viral isolation and thus a specific etiologic diagnosis. PCR affords rapid diagnosis of infections with HSV, CMV, EBV, enterovirus, JC virus, HHV-6, varicella-zoster virus, B. burgdorferi (Lyme disease), Bartonella henselae (cat scratch disease), and HIV. The specificity of PCR in HSV encephalitis approaches 100% and the sensitivity ranges from 75 to 95% depending on the quality of the laboratory (1). PCR has become the gold standard for evaluation of infants and children with suspected HSV encephalitis.

Immunoglobulins and antibodies have limited usefulness for early diagnosis because of poor specificity and sensitivity. Additionally, the antibody response in the CSF does not appear before the fifth day of illness. Finally, acute and convalescent serum antibody titers generally take 3 to 6 weeks to develop.

Electroencephalography (EEG) is usually abnormal in infants and children with encephalitis and shows slowing and epileptiform discharges that can be diffuse or focal. HSV encephalitis classically produces slowing, sharp-wave discharges, or periodic lateralizing epileptiform discharges localized to the temporal or frontal lobe (2). EEG however, is not specific for HSV encephalitis since only 50% exhibit the classic EEG findings. Similar EEG findings have been found with infectious mononucleosis.

Neuroimaging studies, such as computed tomography (CT) or magnetic resonance imaging (MRI), have major roles in evaluating infants and children with presumed or proven CNS infections. Large mass lesions, such as tumors, hemorrhages, and brain abscesses, can be excluded reliably with CT, especially when obtained with contrast enhancement. CT is a better imaging modality for infants with suspected intrauterine viral infections, since small intracranial calcifications are better detected by CT compared to MRI or ultrasound (1). MRI is the preferred imaging modality in children with suspected viral encephalitis and post-infectious encephalomyelitis (1). Herpes simplex encephalitis in older children reveals T2 prolongation on MRI in the medial temporal lobe, orbitofrontal region, or cingulate gyrus, as well as cortical enhancement in these regions when gadolinium is administered intravenously (1,2). In contrast, neonatal herpes simplex encephalitis in the acute stages reveals diffuse brain edema that is consistent with the hematogenous transmission of the virus to the brain. Subsequent imaging shows atrophy, parenchymal calcifications, or cystic encephalomalacia (1).

The definitive diagnostic test of encephalitis, however, is brain biopsy for tissue histology and culture. The utility, however, of routine brain biopsies in children is controversial. Improved neuroimaging techniques and low adverse effects from current antiviral therapy have made empiric therapy the usual practice. Brain biopsy has utility if patients have atypical features or the disease progresses despite empiric therapy (1,2).

Encephalitis and other non-infectious conditions that suggest the presence of CNS infection severe enough to alter the state of consciousness, should be admitted to a Pediatric Intensive Care Unit (PICU) for initial evaluation and supportive care. Severe encephalitis can lead to extensive areas of perivascular infiltrates and diffuse cerebral edema with elevation in ICP and cerebral herniation (2). Frequent assessments of responsiveness, neurological exam, anticipatory monitoring for seizures, and signs of increased intracranial pressure can all be provided in the PICU.

Since antiviral therapy has decreased the mortality for HSV infections by nearly 40% from the pre-antiviral era, acyclovir is the treatment of choice for herpes simplex encephalitis. Antivirals inhibit viral infection by binding with viral nucleic acid and prevent viral replication. The currently approved dose is 30 mg/kg/day IV divided every 8 hours for 14 to 21 days, but some experts recommend increasing the total daily dose to 45-60 mg/kg/day IV divided every 8 hours. Acyclovir has also been effective against varicella zoster virus, while other antiviral agents such as ganciclovir and foscarnet have been used for CMV infections. Unfortunately, antiviral therapy has essentially no impact on morbidity among survivors of CNS disease. Approximately two-thirds still suffer neurological impairment such as major motor and sensory deficits, aphasia, and amnestic syndrome (Korsakoff's psychosis) despite antiviral agents during the acute CNS infection.

Encephalitis from arthropod-borne viruses cannot be treated with specific therapy and typically resolve with conservative management, antipyretics, intravenous fluids, and antiepileptic drugs. Seizures, a frequent complication of viral encephalitis, can be treated acutely with lorazepam and may need maintenance antiepileptic drug therapy with phenobarbital or phenytoin in standard doses.

Potentially life-threatening complications of encephalitis are increased intracranial pressure (ICP), seizures refractory to antiepileptic therapy, and neuronal destruction of the brainstem leading to respiratory compromise or hemodynamic instability. Treatment for increased ICP often requires routine head positioning, osmotic diuresis, fluid restriction, and assisted mechanical ventilation with hyperventilation. Long-acting neuromuscular paralytics for intubation and mechanical ventilation should be avoided since clinical manifestations of seizures will not be evident. Furthermore, neuromuscular blocking agents in patients with impairment of consciousness does not permit repetitive neurological exams and the development of raised ICP may not be evident until intracranial hypertension causes Cushing's triad and possible herniation (2).

Overall, the mortality and morbidity for encephalitis is 3 to 4% and 7 to 10%, respectively. Severity is inversely correlated with the age of onset. Children under the age of one year have a mortality of 40 to 50% (2). Death usually results from cerebral edema or vasomotor instability. Generally, improvement occurs over days to weeks, while focal deficits resolve over a period of months. Neurological morbidity includes: personality changes, behavior disorders, mental retardation, blindness, movement disorders, paretic syndromes, spasticity, and persistent ataxia (1-4). Significant neurological sequelae are more likely to occur if the patient presents with lethargy, coma, or with seizures. Mortality for neonatal HSV encephalitis is 14% with treatment and the outcome is worse for infants with HSV-2 infection (1,3). Older children with HSV encephalitis have mortality at 28% and 40-50% have significant neurological impairment. Of all arboviral encephalitides, Eastern equine encephalitis has the greatest mortality at 50 to 75% with neurological damage in most survivors. In contrast, La Cross encephalitis has the lowest mortality, but seizures develop in 10% of survivors (2).

Questions

1. Encephalitis is usually the result of which of the following:
    a. viral
    b. bacterial
    c. protozoa
    d. autoimmune
    e. fungal
    f. all of the above

2. What are the endemic forms of encephalitis in the United States?

3. Which viral infection involving the CNS is likely to present with focal neurological findings?
    a. HSV
    b. Coxsackievirus
    c. Enterovirus
    d. Rabies virus
    e. St. Louis virus

4. Match the following encephalitis (first column) with the appropriate clinical characteristic (second column):

Japanese encephalitis	SIADH
Eastern equine encephalitis	Decorticate or decerebrate posturing
Post-infectious encephalitis	Aedes triseriatus
St. Louis encephalitis	Multiple levels of CNS involved
La Cross encephalitis	Highest mortality

5. Polymerase chain reaction (PCR) is the diagnostic method of choice for confirming the cause of encephalitis for all of the following except:

a. Cytomegalovirus
b. Enteroviruses
c. HHV-6 and HHV-7
d. HSV 1 and 2
e. Rabies virus

6. True/False: Antiviral therapy has decreased the morbidity and mortality for HSV encephalitis.

Related x-rays

Herpes encephalitis case: Higashigawa KH, Yamamoto LG. A Toxic Infant with Aseptic Meningitis. In: Yamamoto LG, Inaba AS, DiMauro R. Radiology Cases In Pediatric Emergency Medicine, 2002, volume 7, case 9. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v7c09.html

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Answers to questions

1. a. viral
2. HSV, St. Louis encephalitis, and rabies virus.
3. a. HSV
4. Japanese encephalitis-decorticate or decerebrate posturing, Eastern equine encephalitis-highest mortality, Post-infectious encephalitis-involvement of multiple CNS levels, St. Louis encephalitis-SIADH, La Cross encephalitis-Aedes triseriatus.
5. e. Rabies virus
6. False. Antiviral therapy has only decreased mortality, NOT morbidity.

Chapter VI.16. Sepsis
Guliz Erdem, MD

A 13 month old infant presents to the emergency department with a 2 day history of low-grade fevers, runny nose and increasing fussiness. She also developed a rash and vomiting. Her mother notes that the red-purple lesions on her legs have increased in number since this morning.

Exam: VS T 39.6, P 170, R 50, BP 80/50. She is weak, poorly responsive and sick (toxic) appearing with occasional grunting. Her oral mucosa is sticky. Lungs are clear. Heart is tachycardic. Abdomen is scaphoid, without hepatosplenomegaly. Her extremities are slightly mottled with asymmetrical maculopapular and few petechial lesions over upper and lower extremities. Her capillary refill time is delayed (about 3 seconds).

You are worried about meningococcal disease and explain to her parents that you must start parenteral antibiotic treatment and fluid replacement immediately. While trying to obtain IV access, the infant becomes more lethargic and her blood pressure drops further. You place an intraosseous needle and administer fluids, pressor medications and ceftriaxone (a third generation cephalosporin). Despite these measures, she continues to deteriorate, developing large purpuric lesions on her lower extremities. Her laboratory findings reveal thrombocytopenia, prolonged PT/PTT and increased fibrin degradation products (indicative of disseminated intravascular coagulation - DIC). You intubate the patient and transfer her to the ICU. You notice that it has been less than 40 minutes since you first saw this patient (i.e., the deterioration has been quite rapid).

Her blood culture later grows Neisseria meningitidis. Her antibiotic coverage is changed to high dose, intravenous penicillin. A lumbar puncture is normal indicating that she does not have meningitis. She is successfully extubated on the third day of her hospitalization. Most of the purpuric lesions have regressed but she develops necrosis of the 4th and 5th toes of her right foot, which requires amputation.

Meningococcemia is a classical example for severe sepsis. It is classically said that, patients are well at 12 o'clock and dead by 3 o'clock. Early diagnosis and immediate empiric treatment are life saving as in this case. Patients with severe sepsis can develop complications and die even with appropriate antimicrobial and supportive treatments. Each year, sepsis develops in more than 500,000 people in the United States with a mortality rate of 35-45% in adults (1). Sepsis is estimated to be the 13th leading cause of death overall in patients older than 1 year of age. The highest mortality rates in children are among infants. Approximately two thirds of the cases occur in patients hospitalized for other illnesses (e.g., cancer). There are several definitions used to describe the conditions associated with sepsis (1-3):

Bacteremia (or fungemia) is the presence of viable bacteria (or fungi) in the blood. Septicemia is a systemic illness caused by the spread of microbes or their toxins via the blood stream. This means that septicemia is worse than bacteremia. The two terms are not synonymous.

Systemic inflammatory response syndrome (SIRS) is characterized by at least two of the following :

- Oral temperature of >38C (>100.4F) or <36C (<96.8F).
- Tachypnea (Respiratory rate of >60 breaths/min for infants, >50 breaths/min for children) or PaCO2 of <32 torr.
- Tachycardia (Heart rate of >160 beats/minute for infants, >150 beats/minute for children).
- Leukocyte count of >12,000/L or <4,000/L or >10% bands.

SIRS may have an infectious or noninfectious etiology. SIRS that has a proven or suspected etiology is called sepsis. Sepsis syndrome is sepsis with one or more signs of organ dysfunction, hypoperfusion, or hypotension, such as metabolic acidosis, acute alteration in mental status, oliguria, or ARDS (adult respiratory distress syndrome). Septic shock is sepsis with hypotension that is unresponsive or poorly responsive to fluid resuscitation plus organ dysfunction or perfusion abnormalities.

Noninfectious etiologies of SIRS that need to be considered include trauma, adrenal insufficiency, anaphylaxis, burns, bleeding, cardiac tamponade, dissecting or ruptured aortic aneurysm, drug overdose, neoplasms, myocardial infarction, pancreatitis, post-cardiopulmonary bypass syndrome and pulmonary embolism.

The causative organism varies considerably by age. Streptococcus pneumoniae, Neisseriae meningitidis, Staphylococcus aureus, and group A streptococci are major causes of sepsis in children beyond the newborn period. Blood cultures yield bacteria or fungi in 20-40% of cases of severe sepsis and in 40-70% of cases of septic shock.

Although the infection is an essential part of the development of sepsis, the septic response occurs when immune defenses fail to contain the invading microbe(s). Sepsis due to gram negative microorganisms and endotoxic shock are major triggers for the septic syndrome. The lipopolysaccharide (LPS or endotoxin) of gram negative bacteria is transferred to CD14 on the surfaces of phagocytic and polymorphonuclear cells by a LPS binding protein. This interaction triggers the release of mediators, such as TNF-alpha, that further amplify this signal and transmit it to other cells and tissues. Gram positive microorganisms, especially Staphylococcus aureus can elaborate exotoxins, which appear to act through a similar signal pathway to that of endotoxins, triggering the release of inflammatory mediators. How these signals initiate inflammation and how the host responds to them are active areas of research. It has been shown that the inflammation signals are specific to the plasma membranes and a family of proteins named "toll-like receptors" (TLR) are shown to be cellular components of host defense against bacterial challenge. Toll receptors were initially described in Drosophila and shown to activate host defenses against fungal infection in the adult fruitfly. Subsequently, mammalian homologs of these proteins were shown and named as toll-like receptors (TLR). Different members of TLR family may have different roles in inflammation and sepsis. TLR4 appears to confer responsiveness to bacterial lipopolysaccharide (gram negative infections) and TLR2 appears to mediate stimulation by gram positive, gram negative microorganisms and mycobacteria. These proteins basically help the host in transduction of inflammatory signals and they share these pathways (due to their high homology) with the IL-1 receptor in humans. IL-1 is also a critical component of the general inflammatory response.

The septic response then involves complex interactions among microbial signal molecules, leukocytes, humoral mediators and vascular endothelium. Inflammatory cytokines amplify and diversify the overall response. Microbial toxins stimulate the production of cytokines like TNF-alpha and IL-1-beta, which in turn promote endothelial cell-leukocyte adhesion, release of proteases and arachidonic acid metabolites and activation of clotting. IL-8, a neutrophil chemotaxin, may have an especially important role in perpetuating tissue inflammation. IL-6 and IL-10, which are counter-regulatory, inhibit the generation of TNF-alpha, augment the action of acute phase reactants and immunoglobulins, and inhibit T-lymphocyte and macrophage function. IL-6 along with other mediators can also promote intravascular coagulation.

Many tissues may be damaged by the septic response. The probable underlying mechanism is widespread vascular endothelial injury, with fluid extravasation and microthrombosis that decrease oxygen substrate utilization by the affected tissues. Additionally, stimuli such as TNF- alpha induce vascular endothelial cells to produce and release cytokines, procoagulant molecules, platelet activating factor (PAF), endothelium derived relaxing factor (nitric oxide) and other mediators. Moreover, vascular integrity may be damaged by neutrophil enzymes (such as elastase) and toxic oxygen metabolites so that local hemorrhage ensues (4). Nitric oxide is implicated as a mediator septic shock in animals.

The manifestations of sepsis are usually superimposed on the symptoms and signs of the patient's underlying illness and primary infection. Symptoms can be variable. Nonspecific mental status changes and hyperventilation are often the early findings in older children and adults. Irritability, lethargy or confusion can be seen even if meningitis is absent. Young children can exhibit signs of diminished perfusion while maintaining a normal blood pressure, such as delayed capillary refill, weak peripheral pulses, and cool extremities. Nausea, vomiting, diarrhea and ileus can be present. Cholestatic jaundice with elevated levels of serum bilirubin (mostly conjugated) and alkaline phosphatase may precede the other signs. Blood glucose concentration often initially increases as a stress response.

While most patients have fever, some have a normal temperature or are hypothermic. Tachypnea and tachycardia are common signs. Hypotension and DIC, which can complicate sepsis, predispose to cyanosis and ischemic necrosis of peripheral tissues. Other skin lesions such as ecthyma gangrenosum (Pseudomonas aeruginosa), petechial rash (meningococcemia, rarely H. influenzae type B), and purpura fulminans can be suggestive of specific pathogens. The skin and mucosa should be examined carefully and repeatedly for lesions.

Cardiac output is initially normal or increased (the "hyperdynamic phase") in sepsis and helps in distinguishing septic shock from other types of shock. A definitive diagnosis requires the isolation of the microorganism from blood or a local site of infection. At least two and probably three sets of cultures should be obtained. Buffy-coat smear of peripheral blood is a quick and inexpensive method and can assist in more effective therapy; however it is not very sensitive. In early sepsis, abnormalities may include leukocytosis or leukopenia, left shift (with or without toxic granulations), thrombocytopenia, increased lactic acid levels and proteinuria. Active hemolysis suggests clostridial bacteremia, malaria, a drug reaction, or DIC.

With the critically ill child, as in the case scenario, time must not be wasted on performing an extensive diagnostic evaluation. Obtaining a blood culture before initiating antibiotic therapy may be prudent in these children. Other diagnostic labs and a lumbar puncture may be delayed so that antimicrobial treatment can be started immediately in critically ill patients. Severe coagulopathy, as frequently seen in meningococcemia, may also delay lumbar puncture because of the risk of spinal epidural hematoma and bleeding.

Risk factors and prognostic factors include host related factors such as malnutrition, splenectomy, HIV infection, burns, hematologic malignancies and neoplasms; or treatment related factors such as surgical invasive procedures, high dose of corticosteroids or other immunosuppressive drugs, mechanical ventilation, neutropenia and presence of indwelling mechanical devices.

Numerous sepsis scoring systems have been developed in adults and children, particularly for meningococcemia. The best indicator of sepsis and poor outcome is the presence of shock (5). Multiorgan failure is the leading cause of mortality in sepsis patients. The outcome is influenced by the patient's underlying disease and by the microorganism. The outcome is worse in bacteremia caused by Candida and enterococcus species when compared with the coagulase negative staphylococci. Recently, several polymorphisms in genes coding for key inflammatory molecules have been identified and suggested as a risk factor in sepsis and adverse outcomes.

Cardiopulmonary complications include ventilation-perfusion mismatching which produces a fall in arterial pO2 early in the course of sepsis. Increasing alveolar capillary permeability results in an increased pulmonary water content, which decreases pulmonary compliance. Progressive diffuse lung infiltrates and hypoxemia indicate the development of acute respiratory distress syndrome (ARDS). ARDS develops in up to half of adult patients with severe sepsis. Depression of cardiac function (diminished contractility) develops within 24 hours in most patients with advanced sepsis. Although myocardial dysfunction may contribute to hypotension, refractory hypotension is usually due to a low systemic vascular resistance. Death results from refractory shock or the failure of multiple organs.

Renal complications include renal failure following acute tubular necrosis. In some patients glomerulonephritis, renal cortical necrosis or interstitial sepsis can also cause renal failure.

Thrombocytopenia occurs in up to one-third of the patients. Disseminated intravascular coagulation (DIC) may be seen. Prolonged or severe hypotension may induce acute hepatic injury or ischemic bowel necrosis.

If sepsis lasts weeks to months, critical-illness polyneuropathy may develop as a neurologic complication.

Sepsis is a medical emergency and urgent measures for the treatment of infection as well as hemodynamic and respiratory support need to be taken. Priorities in resuscitation of the child who has septic shock mirror those with any other type of shock (6). All children should receive supplemental oxygen. The child in respiratory distress should be intubated. Drugs that cause vasodilation or myocardial depression should be avoided. At least two separate IV lines are required to administer fluids and medications. Intraosseous infusion may be used when peripheral vascular access cannot be obtained rapidly. Cardiovascular support using inotropic medications such as dopamine, dobutamine, and possibly epinephrine, is necessary in almost all patients with severe sepsis.

Empiric antimicrobial therapy should be initiated as soon as blood and other relevant sites are cultured. However, difficulty obtaining cultures should not delay antibiotic administration which must be started as soon as possible. Maximal recommended doses of drugs should be given parenterally. The immune status of the patient, the underlying condition (including illicit injecting drug abuse, splenectomy) are important in deciding the appropriate treatment. Removal of indwelling intravenous catheters and removal or drainage of a focal source of infection are essential. The duration of treatment is influenced by factors such as the site of tissue infection, the adequacy of surgical drainage, the patient's underlying disease and the antimicrobial susceptibility of the pathogen. A typical empiric treatment regimen in children usually includes a third generation cephalosporin and further coverage for gram negative bacteria may be needed such as aminoglycosides, anti-pseudomonal penicillins, extended-generation penicillin with beta-lactamase inhibitor or carbapenems. In areas with increased pneumococcal or staphylococcal resistance or for patients who have received frequent antibiotic therapy (sickle cell anemia) vancomycin can also be started for suspected gram positive infections

Despite aggressive management, many patients with severe sepsis or septic shock will die. Two types of agents that may help in preventing these deaths are being investigated:

1. Drugs that neutralize bacterial endotoxin, thereby potentially benefiting the patients who have gram negative infection.
2. Drugs that interfere with one or more mediators of the inflammatory response and may benefit all patients with sepsis. Recently, activated protein C is approved by FDA for treatment of selected patients with sepsis.

Questions

1. Which one of the following is not a parameter in the definition of SIRS?
    a. Hypotension
    b. Tachycardia
    c. Tachypnea
    d. Leukocytosis
    e. Hypothermia

2. Which is an early finding in septic shock?
    a. Decreased urine output
    b. Increased cardiac output
    c. Decreased blood pressure
    d. Diffuse lung infiltrates

3. A number of different principles apply to the immediate management of a child in septic shock. In general, management should be prioritized in order of urgency. Which of the following is not an immediate priority in the resuscitation phase of a child in septic shock (2)?
    a. Ensure adequate airway support
    b. Correct anemia
    c. Administer volume resuscitation
    d. Cardiovascular support
    e. Empiric antibiotic treatment

4. Which microorganism is a common etiology in endotoxic shock?
    a. Staphylococcus aureus
    b. Streptococcus pyogenes
    c. Streptococcus pneumoniae
    d. Escherichia coli

5. Which of the following skin examination findings is generally not associated with sepsis?
    a. Pyogenic granuloma
    b. Ecthyma gangrenosum
    c. Purpura fulminans
    d. Petechiae

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Answers to questions

1.a, 2.b, 3.b, 4.d, 5.a

Chapter VI.17. Kawasaki Disease

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This is a 2 year old Japanese-Korean male presenting with 5 days of fever up to 39 degrees C (102.2 degrees F). On the second day of illness, he developed red lips and an erythematous maculopapular rash over his torso. By the third day of illness, his conjunctivae were injected without exudates, his rash involved his extremities, and he developed a strawberry tongue. On the fourth day of illness, he had edema to his hands and feet with a diffuse red-purple discoloration over the palms and soles. His lips were now cracked and bleeding. He was noted to be irritable and fussy, with decreased oral intake.

Exam: VS T 39.5, P 130, RR 40, BP 100/60, oxygen saturation 100% in room air. Weight and height are at the 25th percentile. He is alert and slightly fussy, but he consoles easily and he is not lethargic. His bulbar conjunctivae are injected with limbal sparing (less injected around the limbus where the cornea fuses with the conjunctiva), but no exudates. His lips are red and cracked. His tongue is bright red. His neck is supple with bilateral small lymph nodes. Heart is slightly tachycardic, with no murmurs or gallop. Lungs are clear. Abdominal exam finds no abnormalities. He has some mild edema of his hands and feet with some red-purple discoloration of the palms and soles wrapping partially around the dorsum with a sharp demarcation at the wrists and ankles. He has a generalized deeply erythematous rash which is flat with irregularly shaped pink-red lesions ranging from 1 to 7 cm in diameter, with some areas coalescing. The lesions blanch. No joint swelling is noted. He moves all extremities well.

He is admitted to the hospital for further management and treatment of suspected Kawasaki Disease (KD). Lab: CBC WBC 19,500 with 75% segs, 20% lymphs, 5% monos. Platelet count 475,000. Hgb 10. AST 56, ALT 62, bilirubin 1.2, albumin 2.8. Urinalysis with WBC 5-10, no organisms, negative for protein, blood, leukocyte esterase or nitrites. Urine and blood cultures are obtained. Echocardiogram and EKG are both normal.

He is treated with IVIG (IV gamma globulin) and aspirin. His fever defervesces after 24 hours with improvement in his rash, lips, extremities and conjunctivae. He is discharged after the completion of IVIG treatment. Follow-up echocardiograms demonstrate no abnormalities.

Kawasaki Disease (KD) is an acute multisystem vasculitis that almost exclusively affects young children. First described by Dr. Tomisaku Kawasaki of Tokyo, Japan in 1967, it occurs in all regions of the world among children of diverse ethnicity. Significant adverse cardiac effects were recognized in untreated patients, particularly the development of coronary artery aneurysms leading to myocardial infarction (thrombosis) and sudden death. The clinical criteria he described remains the basis of all clinical and epidemiologic descriptions used today (see Table 1).

The etiology of KD remains unknown. The acute, febrile, and self-limited nature of KD and its clinical manifestations of rash, meningeal, hepatic, joint, and mucous membrane inflammation strongly suggest an infectious etiology or trigger. The predominance of cases in children under 12 years of age and the occurrence of community-wide epidemics further suggest that the etiologic agent may be common and widely distributed. Despite lack of the identification of an etiologic agent, intravenous gamma globulin (IVIG) has been discovered as a remarkably effective treatment resulting in rapid clinical improvement and prevention of coronary artery sequelae.

KD has a peak incidence in the first two years of life. In our experience here in Hawaii, peak incidence occurs between 1 to 2 years of age. Fifty percent of patients are younger than 2 years of age and 80% are younger than 4 years (1). The disease infrequently occurs in children greater than 8 years of age. Boys are affected more often than girls by a ratio of 1.5 to 1. Although classic symptoms can occur in children as young as several weeks old, diagnosis within the first 3 months of life is uncommon, perhaps because of passive protection from maternal antibodies or because these children tend to have atypical or mild clinical manifestations.

Children of Japanese and Korean ancestry are at greatest risk for KD. Children of other Asian or African ancestry have also demonstrated significantly higher incidence rates than those of European ancestry. In Hawaii, the rate for children of European ancestry is 9 per 100,000 per year; for children of African-American ancestry 20 per 100,000 per year; and for children of Japanese and Korean ancestry 145 per 100,000 per year (1).

KD occurs more frequently in the winter and the spring than in the summer and fall. Community-wide outbreaks have been noted, but there is little evidence of person-to-person spread or of point source exposure in these outbreaks.

Pathologically, KD is a multisystem vasculitis with a predilection for the coronary arteries. The acute phase (first 10 days of illness) is characterized by an intense inflammatory infiltrate in the vasa vasorum of the coronary arteries with infiltration and hypertrophy of the intima. Pancarditis may be present and the pericardium may also inflamed, often with effusion. Some patients may develop congestive heart failure and myocardial dysfunction, but death during this phase is usually sudden and thought to be due to arrhythmia. During the convalescent phase (10-40 days after the onset of fever) the inflammatory infiltrate matures from predominantly polymorphonuclear leukocytes to a predominance of mononuclear cells. Fragmentation of internal elastic lamina and damage to the media can result in aneurysm formation. Coronary artery involvement is usually bilateral and most severe near the origin (proximal). Death is most frequently due to acute myocardial infarction due to acute coronary artery thrombosis during this stage.

Late changes (>40 days) involve healing and fibrosis in the coronary arteries. There may be organizing thrombosis within aneurysms with recanalization, calcification and stenosis. Fibrosis can also occur in the myocardium from old myocardial infarction. Death during this stage most often occurs from acute myocardial infarction or chronic myocardial ischemia.

The immunologic mechanisms causing KD vasculitis are partially understood involving abnormalities of T cells, B cells, cytokines, autoantibodies, macrophages, monocytes, and blood vessel associated matrix metalloproteinases.

There is no pathognomonic diagnostic test for Kawasaki syndrome. The diagnostic criteria for the diagnosis of KD as established by Dr. Kawasaki have stood the test of time and are listed in Table 1 and described in detail below.

Table 1 - Diagnostic Criteria for Kawasaki Disease

1. Fever
2. Conjunctival vascular injection
3. Mouth changes:
   a. Erythema, cracking and bleeding of lips
   b. Strawberry tongue
   c. Oropharyngeal erythema
4. Polymorphous erythematous rash
5. Changes in the hands and feet consisting of:
   a. Indurative edema
   b. Diffuse erythema of the palms and soles
   c. Convalescent desquamation after day 10
6. Unilateral lymphadenitis (>1.5 cm diameter)

Clinical Course: The onset of illness is often abrupt with fever as the initial sign. The fever is typically persistent and high ranging between 38 and 41 degrees C (101 to 106 degreesF). Initially the criteria stated that fever should exceed 5 days before making the diagnosis. With recognition of serious sequelae if therapy is delayed, we now stress making the diagnosis as early as possible, disregarding the 5 day provision. In untreated patients, the mean duration of fever is 11 days with a range of 5 to 33 days. Within 2 to 5 days of fever onset, the child develops the other diagnostic signs of KD. These children are often exceedingly fussy or irritable. The eye involvement consists of discrete vascular injection of the bulbar conjunctiva most marked in the periphery with relative sparing around the limbus (known as limbic or perilimbic sparing). Exudate is absent while photophobia may be present. Mild anterior uveitis may be present. Mouth changes include initial bright red erythema of the lips (progressing to swelling, cracking and bleeding), prominent papillae on the tongue with erythema (strawberry tongue), and diffuse erythema of the oropharynx without vesicles, ulcers or erosion. The rash can takes many forms (which is why the term "polymorphous" is used) but it is never vesicular or bullous. The most common form is deeply erythematous with papules varying from 2-3 mm to large, coalescent plaques covering several centimeters. Frequently it is pruritic and appears urticarial. A diffuse maculopapular measles-like rash is also commonly seen. Erythema marginatum and diffuse scarlatiniform erythroderma are seen less frequently (<5%). Rash distribution is variable. It frequently involves the face, often coalescent and mask-like around the eyes, nose and mouth. It can involve the perineum with later peeling. It may be distributed more prominently on the trunk or the extremities. The rash is not fixed and can clear then reappear in new areas. It may be more prominent with high fever. Changes in the hands and feet consist of firm, indurative edema with diffuse red-purple discoloration of the palms and soles, usually with sharp demarcations at the wrists and sides of the hands and feet. In early convalescence (10-20 days after onset of fever), desquamation starts just under the nails and progresses to involve the entire palms and soles, with skin peeling in sheets. Cervical lymph node involvement occurs in approximately 50 % of patients, characterized by a sudden onset of unilateral firm swelling measuring more that 1.5 cm in diameter. Occasionally the cervical adenopathy can be diffuse and massive, even causing tracheal shift. It can be moderately tender, with or without erythema, and non-fluctuant.

Associated findings include aseptic meningitis with CSF pleocytosis in 25% of patients. CSF counts range between 50-150 per cubic mm (mostly mononuclear). CSF protein levels are normal to slightly elevated, with normal glucose. Urethritis and sterile pyuria are present in approximately 60% of patients. Some hematuria may be seen, but urinary protein is usually normal. A small meatal ulcer or meatitis (redness) of the urethra is often seen in males. Prior to the use of IVIG, approximately one third of patients developed arthritis. During the first week of illness, arthritis was usually polyarticular of large and small joints. Oligoarthritis of large weight bearing joints was noted more in the second week of illness. Late onset arthritis has been virtually eliminated with the use of IVIG. Severe abdominal pain, often associated with diarrhea can be seen in the first few days of illness. Occasionally it may present as an acute abdomen. Amylase and lipase levels may be elevated, suggesting an acute pancreatitis. Liver involvement occurs in 40% of patients, including liver enzyme and bilirubin elevations. The direct fraction of bilirubin can be elevated suggesting a primarily obstructive pattern. Gallbladder hydrops can be seen with elevated bilirubin levels and findings of a right upper quadrant mass. Ultrasonography can confirm the diagnosis. This is usually a self-limited complication and does not require surgery, resolving within 2 weeks with IVIG and aspirin therapy.

A wide spectrum of cardiac abnormalities has been identified. Many children have tachycardia. Some develop signs of congestive heart failure ranging from mild pulmonary vascular congestion and a gallop rhythm to cardiogenic shock. About a third of patients may have pericardial effusions during the first week of illness. Mitral and tricuspid insufficiency have also been noted. Echocardiography may demonstrate some degree of myocardial involvement in the majority of patients. Prolongation of the PR interval and first-degree heart block are common, but more significant arrhythmias are rare. Many of these abnormalities resolve rapidly after IVIG therapy.

Coronary artery abnormalities can be detected by echocardiography at the end of the first week to the second week of illness (range 7-28 days after onset of illness). Progressive dilatation and aneurysm formation may occur with a peak incidence and severity at approximately 1 month after the onset of disease. Prior to the use of IVIG therapy, about 18-25% of patients developed coronary artery aneurysms, with the highest risk in males and children under the age of 1 year. Transient coronary artery dilatation is even more common affecting at least 60%. Regression of aneurysms is common for all but giant aneurysms. Approximately 2/3 of children with aneurysms at 8 weeks post onset have regression by 1 year on echocardiography. Although the aneurysm may appear to have regressed by echo, the vessel walls are not normal and no longer dilate in response to exercise or drugs. These patients may still develop stenosis, tortuosity, and coronary artery thrombosis. Some of these children will develop giant coronary aneurysms (>8mm). Children with coronary abnormalities are at high risk for myocardial infarction, sudden death, coronary thrombosis, and myocardial ischemia within the first year after onset and have a higher lifetime risk in the long term. Giant aneurysms (greater than 8 mm or the diameter of the aorta) pose a most severe problem. These occur in 3% to 7% of untreated patients, are correlated with duration of fever >2 weeks and have a poor prognosis. Children with giant coronary aneurysms are at the highest risk for early myocardial infarctions and sudden death due to coronary thrombosis or rupture. Progression to significant coronary stenosis with resultant myocardial ischemia occurs in a very high percentage over the next 20 years.

Some patients may have more severe vasculitis with acute KD. Aneurysms in vessels other than the coronary arteries, such as axillary, mesenteric, and renal arteries have been noted in severe cases. Some cases develop peripheral gangrene due to severe vasculitis and thrombosis. In infants, fatal KD is indistinguishable from infantile polyarteritis nodosa.

Laboratory findings in KD are nonspecific but consistent with significant inflammatory indices. There is no diagnostic test for Kawasaki disease. Erythrocyte sedimentation rate, C-reactive protein, and alpha-1-antitrypsin are elevated. White blood cell count (WBC) is often elevated with a polymorphonuclear cell predominance and sometimes, a left shift. The WBC rises through the first two weeks of illness, peaking between 7-12 days. By day 5 of illness, 50% of patients have platelet counts greater than 450,000 per cubic mm. By day 10, nearly all have elevated platelet counts which may peak at 650,000 to 2,000,000 per cubic mm between days 10 and 20. Mild to moderate anemia is common. Liver enzymes are moderately elevated (over twice the upper limit of normal) in 40% of patients in the first week. Bilirubin may be elevated in 10% of patients. Hypoalbuminemia is common. Urinalysis shows sterile pyuria in 60%.

Work up of patients suspected of KD should include the above lab studies, and a cardiovascular evaluation including EKG, echocardiography, and chest x-ray.

The differential diagnosis for KD includes staphylococcal and streptococcal toxic shock syndromes, streptococcal scarlet fever, staphylococcal scalded skin syndrome, measles, febrile viral exanthems, adenovirus infection, hypersensitivity reactions (including Stevens-Johnson syndrome, erythema multiforme minor and serum sickness), and systemic onset juvenile rheumatoid arthritis. When KD is suspected, appropriate testing for viral and bacterial infection are indicated in addition to laboratory testing described above.

The diagnosis of KD relies primarily on clinical features and a pattern of non-specific laboratory tests. Since there is no specific diagnostic test available, patients who have a milder illness or an incomplete/atypical pattern of symptoms, may not be diagnosed with KD, but are still at risk for coronary artery disease. These "incomplete" cases are at risk for coronary complications, especially since they may not be diagnosed or treated with IVIG. Infants younger than 6 months of age, and older children are at particular risk. If a child has fever and 2 or 3 of the other criteria PLUS compatible laboratory findings KD should be considered and if needed, expert consultation sought. KD should also be considered in all younger children with fever of unknown origin.

Patients with KD who present with fever and lymphadenitis as the first sign may also pose a diagnostic problem. These patients may be initially diagnosed with lymphadenitis and are treated with antibiotics. The subsequent development of rash, conjunctival injection, mouth, hand and feet changes, may be mistakenly attributed to antibiotic hypersensitivity.

The child who is not of Asian ethnicity may not be diagnosed even with complete clinical signs. Many physicians consider KD to be a disease occurring only in Asians or in high risk areas. KD is severely underdiagnosed across the world where it occurs in children of every racial and ethnic group.

Laboratory tests can be very helpful in the diagnosis although none provide definitive answers. By day 5 of illness, most patients have WBC of 15,000 or more, significantly elevated sedimentation rate (ESR) and C reactive protein (CRP), and platelet count of >400,000. Sixty percent have sterile pyuria with >10 WBC/hpf and 40% have liver enzyme values equal to or greater than 2X the upper limit of normal. Most viral illnesses and serum sickness have normal or low WBC, and normal or near normal ESR and CRP values. Creatinine elevation is unusual in KD and usually suggests another diagnosis.

Since the late 1980s multiple studies have shown that the use of high dose IVIG given in the first 10 days of illness has dramatically altered the clinical and pathologic course of the illness. Prompt clinical improvement follows IVIG: 60% become afebrile within 12 hours of IVIG, and 90% within 48 hours. The risk of coronary aneurysms has been lowered from 18-25% to 2-4%. Infants younger than 1 year of age have the highest risk of coronary abnormalities when untreated. Even with IVIG treatment, the risk of coronary abnormalities at 8 weeks is 15%. For all age groups treated with IVIG, the incidence and severity of any coronary disease and the frequency of giant aneurysms has been greatly reduced.

Once a diagnosis of KD is made, therapy consists of intravenous infusion of IVIG 2 gm/kg given over 10-12 hours. Heart rate and blood pressure should be monitored closely. Patients who remain febrile or have recurrent fevers 48 hours after the end of the initial IVIG infusion, may require an additional infusion. In our experience, approximately 10 % of children require second doses. Expert opinion should be sought for patients who are unresponsive to IVIG as this is the group who develop coronary disease.

Aspirin therapy should be instituted on the day IVIG is given. In the United States, a dose of 100 mg/kg to a maximum of 4 grams per day is given until a few days after defervescence or until the 14th day of illness. This is followed by a daily dose of 3 to 10 mg/kg/day (one half to one 81 mg tablet) until the ESR and platelet counts return to normal, usually about 2-3 months after onset of illness. Aspirin has been shown to result in a more rapid defervescence, lower frequency of relapse of fever and shorter hospital stay. Anti-coagulation with low dose aspirin therapy helps prevent the thrombosis in the setting of vascular inflammation and elevated platelet counts. Serum salicylate levels should be obtained if symptoms of salicylate toxicity develop. Aspirin therapy can be interrupted in children who develop varicella or influenza during the follow-up phase to decrease the risk of Reye syndrome.

There is no data to guide therapy of patients suspected of having KD who present more than 10 days after onset of illness. If patients are still febrile or have other signs of active disease such as progressive coronary artery dilatation, IVIG therapy may result in prompt clinical improvement. Patients who have become afebrile and have normal coronary arteries by 3-4 weeks after illness onset are unlikely to benefit from IVIG and should be placed on low dose aspirin. In patients who have already developed coronary aneurysms without active inflammation, there appears to be no beneficial effect of IVIG.

In summary, KD is a severe acute febrile exanthematous illness of young children, who are usually under the age of 6 years. Cardiovascular damage sustained during the acute and early convalescent phases of KD occurs in over 30% and may be serious, causing lifelong coronary abnormalities including premature myocardial infarction, coronary and myocardial insufficiency or coronary artery rupture. KD is fatal in 2-4% of undiagnosed and untreated patients. Early IVIG therapy results in prompt clinical improvement and prevents coronary artery damage and long term cardiovascular complications. Therefore KD must be recognized, diagnosed and treated early and aggressively. If there is any question about the diagnosis of KD or if a patient thought to have KD does not respond to IVIG and aspirin therapy within 48 hours, expert consultation with a local or national expert is indicated on an urgent basis.

Questions

1. What are the diagnostic criteria for KD?
2. What change in the treatment of KD has been primarily responsible for decreasing the incidence of coronary artery aneurysms in KD?
3. Which children are at higher risk for coronary artery aneurysms?
4. Name some common allergic reactions that may resemble KD?
5. Name some common infections that may resemble KD?

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Answers to questions

1. Presence of fever ranging between 38 and 41 degrees C, and four out of five principal diagnostic criteria which include: discrete conjunctival injection without exudates, changes in the mouth, polymorphous erythematous rash, changes in the hands and feet, and unilateral cervical lymphadenopathy.
2. Intravenous gamma globulin treatment.
3. Children <1 year of age and those untreated with IVIG.
4. Stevens-Johnson syndrome, erythema multiforme, serum sickness.
5. Measles, adenovirus, toxic shock syndrome, scarlet fever, staphylococcal scalded skin syndrome.

Chapter VI.18. Staphylococcal and Streptococcal Toxic Shock Syndromes

Judy Makowski Vincent, MD

A 16 year old girl in previously good health became ill 2 days ago with fever to 39 degrees, myalgias, abdominal pain, and profuse vomiting and diarrhea. Yesterday she noticed a sunburn-like rash that covered her entire body but was most intense on her inner thighs and her palms and soles. This morning she was unable to get out of bed due to feeling "too sick", and when she was helped to stand, she nearly fainted from "light-headedness". She is having her menstrual period and is wearing a tampon.

Exam: T 32.2, P 160, RR 30, BP 60/40 supine. She is an ill-appearing adolescent female who is poorly oriented to her surroundings and only responds to questions with much coaxing, and her answers are incoherent. Her conjunctivae are injected. She has oral mucosal hyperemia and hypertrophy of her tongue papillae. Her tonsils are not enlarged. Total body erythroderma is noted, most pronounced on the inner thighs, and palms and soles, with prolonged capillary refill time of about 6 seconds. Her neck is supple. Her heart exam demonstrates tachycardia with a I/VI systolic ejection murmur without radiation. S1 and S2 are normal with no gallops. Her lungs are clear. Her abdomen is soft and nontender, with hyperactive bowel sounds. She is drowsy and disoriented. Her strength is weak, but her DTR's are normal. Her genitalia exam (normal Tanner 4) is significant for a tampon in the vagina and menses are noted without any other type of discharge. The tampon is removed and sent for culture.

Labs: CBC with WBC 16,000, H/H: 12/36, 50% segs, 30% bands, 15% lymphs, 5% monos, platelet count 70,000. Na 140, K 4.0, Cl 110, bicarbonate 12, BUN 20, Creatinine 0.6, AST 30, ALT 40.

She is given an IV fluid bolus and a dopamine infusion. Her blood pressure, perfusion and mentation improve. IV clindamycin and vancomycin are administered. She is hospitalized in the ICU, where her condition gradually improves. Culture of her tampon grows 4+ Staphylococcus aureus the next day. Her blood cultures are negative.

Simple or trivial skin infections or mere colonization with Staphylococcus aureus may produce toxin-mediated life-threatening disease known as staphylococcal toxic shock syndrome (TSS). This syndrome was first described by Todd et al. in 1978 who reported seven children aged 8 to 17 years who had high fever, headache, vomiting, watery diarrhea, oliguria, and a propensity to acute renal failure, hepatic abnormalities, disseminated intravascular coagulation, and severe prolonged shock (1). S. aureus related to phage-group I was isolated from mucosal (nasopharyngeal, vaginal, tracheal) or sequestered (empyema, abscess) sites, but not from blood. The illness was associated with the isolation of Group 1, type 29 staphylococci from skin, abscesses, empyema fluid or mucous membranes, and Todd named the disease "toxic shock syndrome" (1).

Between 1980 and 1986, 2960 cases of staphylococcal TSS were reported to the CDC, 90% of which were associated with menses. In 1980, a link was discovered between the use of newly introduced superabsorbent tampons and staphylococcal TSS. One brand was removed from the market and all tampons containing superabsorbent polyacrylate fibers were removed in 1985. Non-menstrual staphylococcal TSS also occurs in women, men and children (2,3). Menstrual and non-menstrual TSS are similar in their clinical appearance, but they differ in their target populations and in their outcomes. The prevalence of menstrual TSS has decreased markedly with the institution of preventive measures. Non-menstrual TSS has decreased less dramatically, and now accounts for about one-third of all staphylococcal TSS cases (3).

Menstrual TSS occurs at a rate of 1 per 100,000 menstruating women per year, and 99% of menstrual TSS occurs in women who use tampons (2). The current incidence of staphylococcal TSS has decreased greatly from the early 1980's, which is probably due to greater awareness of its presentation and the removal from the market of hyperabsorbent tampons (4). Risk factors for menstrual TSS include adolescence, lack of antibody to TSST-1 or staphylococcal enterotoxins, Caucasian ethnicity, continuous tampon use, and high absorbency potential of the tampon. Risk factors for non-menstrual TSS include any interruption of the integrity of the skin, mucous membrane colonization with a toxin-producing S. aureus isolate, or any S. aureus infection (2,3).

Todd et al. realized that their patients had clinical features similar to other known staphylococcal toxin related diseases, such as staphylococcal scalded skin syndrome and staphylococcal food poisoning (1). Also, S. aureus was isolated from 2 patients at foci of infection but not from the blood, cerebrospinal fluid, or urine, and an association with staphylococcal toxin was investigated. All staphylococcal strains isolated by Todd elaborated a previously undescribed epidermal toxin which produced a cleavage at or below the basal layer of the skin. Unlike exfoliatin, this new toxin was inactivated by heating to 60 degrees C for 30 minutes and was neutralized by staphylococcal antitoxin, but not by exfoliatin antitoxin (1). All of the staphylococcal isolates in Todd's patients reacted with group-I phages. This unique epidermal toxin has been named staphylococcal toxic shock syndrome toxin-1 (TSST-1). Expression of TSST-1 is determined by oxygen, temperature, pH, and glucose levels (5). It belongs to a large family of toxins called pyrogenic toxin superantigens which are potent stimulators of the immune cell system (i.e., cell mediated immunity), pyrogenicity, and enhancement of endotoxin shock.

Eighteen percent of healthy children and 1% to 5% of healthy menstruating women are colonized with TSST-1-producing strains of S. aureus. These healthy individuals have antibody to TSST-1, but patients with staphylococcal TSS have decreased or absent levels of anti-TSST-1 or anti-enterotoxin antibody, suggesting that anti-TSST-1 and anti-enterotoxin antibodies are protective or mitigating against staphylococcal TSS (2).

Staphylococcal toxic shock syndrome is an illness with the following clinical manifestations (6):

1) Fever with a temperature greater than 38.9 degrees (102.0 degrees F).

2) Rash, which is a diffuse macular erythroderma. In some patients with tampon-associated menstrual TSS, the rash is more intense on the medial aspect of the thighs.

3) Desquamation which occurs 1-2 weeks after onset of illness, particularly on the palms and soles.

4) Hypotension with a systolic blood pressure less than 90 mmHg for adults or less than the 5th percentile for children, or an orthostatic drop in diastolic blood pressure greater than 15 mmHg from lying to sitting, orthostatic syncope, or orthostatic dizziness.

5) Multisystem involvement with three or more of the following: a) Gastrointestinal: Vomiting or diarrhea at the onset of illness. b) Muscular: Severe myalgia or creatine phosphokinase level at least twice the upper limit of normal. c) Mucous membranes: Vaginal, oropharyngeal, or conjunctival hyperemia. d) Renal: Blood urea nitrogen or creatinine at least twice the upper limit of normal, or urinary sediment with pyuria in the absence of urinary tract infection. e) Hepatic: Total bilirubin, alanine aminotransferase or aspartate aminotransferase enzyme levels at least twice the upper limit of normal for laboratory. f) Hematologic: Platelet count less than 100,000. g) Central nervous system: Disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent.

6) Laboratory Criteria: Blood and CSF cultures are generally negative if done. Positive cultures for S. aureus may identify the source of the toxin-producing staph. Serologic tests for Rocky Mountain spotted fever, leptospirosis, or measles are negative.

7) A case is classified as probably TSS if five of the six clinical findings described above are present. A case is classified as confirmed if all six of the clinical findings described above are present, including desquamation, unless the patient dies before desquamation occurs.

The focus of the staphylococcal infection may appear surprisingly normal or may have only minimal signs of inflammation or purulence, such as with impetigo or paronychia. The toxin interferes with the release of inflammatory mediators, so signs of inflammation may be absent (2). Thus it is very important to carefully inspect the skin to identify a possible focus of staphylococcal infection that lacks the typical erythema, warmth, and edema of these infections. Bass et al. have speculated that formes frustes, or mild versions of staphylococcal TSS may exist, which may not have hypotension, for example, but do have the other clinical features of staphylococcal TSS (7).

Five to 7 days after the onset of symptoms, patients with staphylococcal TSS exhibit a desquamating rash. It progresses to full thickness peeling by days 10 to 12. The desquamation begins on the trunk and extremities before localizing to fingers, palms, toes and soles. This desquamation is at or below the basal layer. It may be helpful diagnostically when desquamation occurs, since S. aureus is almost never cultured from the blood or CSF of patients with staphylococcal TSS, and it may not be recovered from any site.

The differential diagnosis of a severe systemic illness with fever and erythematous rash includes: invasive group A streptococcal diseases, Staphylococcal toxin-mediated diseases, septic shock of other bacterial etiologies including meningococcemia, scarlet fever, Rocky Mountain spotted fever, Kawasaki syndrome, leptospirosis, measles, systemic lupus erythematosus, Stevens Johnson syndrome, Epstein-Barr virus, adenovirus infection, enterovirus infection, human parvovirus B19 infection, Yersinia pseudotuberculosis infection (Izumi fever), drug reactions, juvenile rheumatoid arthritis, polyarteritis nodosa, Reiter's syndrome, mercury poisoning, etc.

Early recognition of staphylococcal toxic shock syndrome with intervention by removing the focus of infection and providing intravenous fluids and appropriate antibiotics before shock develops may preclude the development of shock and multiple organ failure, which in this disease appears to be secondary to shock (7). With this approach, mortality has decreased significantly below the 10% level observed in the epidemics reported in the early 1980s. The presence of cardiovascular compromise with either myocardial depression and or vascular instability should be treated with appropriate inotropes and/or vasoactive pressors in addition to fluids in an intensive care unit. Antimicrobial therapy should be selected with knowledge of the local rate of methicillin resistance. If the rate of methicillin resistance is significant, IV vancomycin and clindamycin are preferred over anti-staphylococcal penicillins and cephalosporins. Additionally, anti-ribosomal antibiotics such as clindamycin inhibit protein synthesis which may reduce the rate of toxin excretion.

Non-menstrual TSS has a higher mortality rate than menstrual TSS (3,8). Multiorgan failure, particularly renal failure and adult respiratory distress syndrome, are major sequelae of staphylococcal TSS. Unlike streptococcal TSS, in which multiorgan failure is present on admission or within a few hours of admission, multiorgan failure due to staphylococcal TSS tends to occur slightly later in the course of hospitalization. It may occur well after the acute phase of illness. Death is usually due to shock, cardiac arrhythmias, or bleeding abnormalities. In cases of non-fatal staphylococcal TSS, the patient usually improves quickly. After hypotension responds to therapy, respiratory, cardiac, renal and hepatic abnormalities improve quickly and without permanent sequelae (2,3). In cases of prolonged hypotension, chronic renal failure may result. Patients may experience persistent pain, weakness, and fatigue. There may be permanent cognitive impairment, such as memory loss, distractibility, emotional or personality alteration, and persistently cyanotic extremities (2,3).

Menstrual TSS has a risk of recurrence (2). It may recur multiple times in a patient, with each recurrence of decreasing severity. This phenomenon may be due to a delayed or low-level expression of anti-TSST-1 or anti-enterotoxin antibody (2). Women who have had a previous episode of menstrual TSS should be advised to discontinue tampon use and barrier contraceptive methods such as diaphragms. Additionally, some physicians prescribe prophylactic antibiotics to these women during menstruation. Recurrence after non-menstrual TSS is uncommon (2,3).

Since staphylococcal toxic shock syndrome and streptococcal toxic shock-like syndrome are both serious life-threatening diseases that can develop from minor skin infections and fatal consequences can develop in hours, constant vigilance and concern must be maintained when treating staphylococcal and streptococcal skin infections. The serious consequences of staphylococcal and streptococcal toxic shock syndromes demand early recognition of symptoms and aggressive treatment.

A common scenario is a febrile child with impetigo or secondarily infected varicella lesions, who presents with an erythroderma. Early toxic shock syndrome should be considered. Laboratory studies should be obtained, but these may not be very helpful in diagnosing early toxic shock. It may be best to administer parenteral antibiotics in the outpatient setting and observe the patient for several hours in the office or emergency department. Any worsening would suggest toxic shock syndrome. If any uncertainty exists, it is reasonable to hospitalize these patients.

Streptococci can also cause toxic shock syndrome. Virulent group A beta-hemolytic streptococci (GABHS) strains were prevalent in the early part of this century in the pre-antibiotic era when fatal scarlet fever was common. These virulent strains became less prevalent after the 1950s, then recently reappeared. In the late 1980s several reports of outbreaks of rheumatic fever occurred across the United States after a marked decline in the incidence of the disease over the previous four decades. Along with these outbreaks came reports of numerous individuals who had invasive fulminant infections with GABHS with septicemia, shock, and multiple organ failure. A high mortality was reported. Some of the individuals had skin and mucous membrane findings similar to those seen in staphylococcal TSS, and subsequently streptococcal TSS was identified (9,10,11).

To determine whether these isolated reports represented an increasing incidence of invasive GABHS disease, Hoge et al. performed a retrospective review of invasive cases of GABHS disease in Pima County, Arizona over a 5-year period (12). Reporting an annual incidence of 4.3/100,000, they found that the incidence of severe infection and death due to GABHS disease was increasing, and that those affected tended to be younger and healthier than in the past. In a prospective, population-based study, Zurawski et al. reported similar results in Atlanta with a 5.2/100,000 annual incidence (13).

Hoge's study resulted in a clinical case definition for invasive GABHS disease, which has recently been updated (14). Risk factors for invasive GABHS disease are diabetes, cardiovascular disease, alcoholism, neurologic disease (paraplegia, dementia), chronic pulmonary disease, intravenous drug use, cirrhosis, malignancy, dialysis, use of corticosteroids or other immunosuppressive medications, rheumatoid arthritis, recent varicella infection, human immunodeficiency virus infection, lack of skin integrity, recent surgery, abortion, childbirth, and obesity (12,15).

Most outbreaks of invasive GABHS disease in communities do not represent common-source outbreaks, but rather are a clustering of sporadic cases (15). These severe, invasive forms of GABHS disease do not usually follow episodes of acute GABHS pharyngitis (10,16). No focus of infection is identified in 20-25% of cases. Zurawski et al. determined that use of nonsteroidal anti-inflammatory drugs (NSAIDS) in the week prior to the diagnosis of invasive GABHS disease was statistically associated with mortality (13); however other studies have not established this relationship.

The pathogenic mechanisms of invasive GABHS infections are complex and have not yet been completely defined (10,13,17,18).

Streptococcal TSS is a severe illness associated with invasive or noninvasive group A streptococcal (Streptococcus pyogenes) infection. Streptococcal TSS may occur with infection at any site but most often occurs in association with infection of a cutaneous lesion. Signs of toxicity and a rapidly progressive clinical course are characteristic, and the case-fatality rate may exceed 50% (19).

The prodromal illness of streptococcal TSS is nonspecific and includes symptoms such as fever and myalgia. Therefore clinicians may not have reason to suspect group A streptococcal infection when they are confronted with a patient appearing to have signs of toxicity with shock and multiorgan failure following a nonspecific prodromal illness. This may lead to delay in the diagnostic workup and institution of definitive therapy.

There is often a history of minor trauma preceding the prodromal illness. This trauma is of such a minor nature as to seem inconsequential, such as falling off a small children's swingset or tripping over a toy while running. It has been postulated that this minor trauma may become a locus minoris resistensiae, a site of lessened resistance, allowing GABHS in the bloodstream to focalize and multiply (20).

The earliest clue that a patient has streptococcal TSS is often the presence of multiorgan failure either at the time of presentation or soon after admission to the hospital. The kidneys are among the first organs to fail. Renal impairment is present early in the hospital course and precedes hypotension in 40-50% of patients (10). The physical examination is remarkable for shock. Examination of the skin initially reveals cool, clammy skin with poor perfusion, which progresses to mottling and purpura. Worsening of perfusion and shock may lead to tissue necrosis and frank gangrene.

Early clues in the laboratory evaluation of streptococcal TSS are hemoglobinuria and serum creatinine values that are on average more than 2.5 times normal (10). Hypocalcemia and hypoalbuminemia are present on admission and coexist throughout hospitalization (10). Serum creatinine kinase may be helpful in detecting underlying tissue involvement and destruction; when the level is elevated or rising, there is good correlation with underlying necrotizing fasciitis or myositis (10). Blood cultures are usually positive for GABHS within 24 hours or less after collection.

The prodrome of staphylococcal TSS nearly always includes gastrointestinal symptoms such as vomiting, diarrhea, and abdominal pain; the prodrome of streptococcal TSS only rarely includes these symptoms.

Patients with staphylococcal TSS are less likely to have multiorgan failure at the time of hospital admission, whereas multiorgan failure on or within hours of hospital admission occurs frequently with streptococcal TSS. We believe that with early recognition of a staphylococcal toxin-related illness, hypotension may be averted by administration of fluids and antibiotics. However, fluids and antibiotics do not appear to prevent shock in streptococcal TSS. We believe that the multiorgan failure of staphylococcal TSS may be a secondary effect of hypoperfusion due to shock, whereas the multiorgan failure of streptococcal TSS may be due to a primary effect of the toxin.

Streptococcus pyogenes remains exquisitely sensitive to penicillin. However some studies have reported mortality rates from invasive GABHS disease as high as 80% despite treatment with penicillin. In 1952 Eagle demonstrated a reduced efficacy of penicillin with high inoculum size (21). This has subsequently been named "the Eagle effect". In 1988 Stevens et al. compared the use of penicillin, erythromycin and clindamycin in GABHS myositis in mice and demonstrated that penicillin-treated mice fared no better than untreated controls if penicillin treatment was delayed for as little as 2 hours (22). Erythromycin-treated mice fared better than penicillin-treated mice and untreated controls, but only if treatment was started within 2 hours. However clindamycin-treated mice had survival rates of 100%, 100%, 80%, and 70%, even if treatment was delayed for 0, 2, 6, and 16.5 hours respectively (22).

Clindamycin is superior to penicillin in the treatment of invasive GABHS disease (10) because its efficacy is not affected by inoculum size or stage of growth. Clindamycin is a potent suppressor of bacterial toxin synthesis and it facilitates phagocytosis of GABHS by inhibiting M-protein synthesis. Clindamycin suppresses synthesis of penicillin-binding proteins and it has a longer post-antibiotic effect than beta-lactams. Clindamycin suppresses lipopolysaccharide-induced monocyte synthesis of TNF-alpha.

The patient with suspected invasive GABHS disease should be admitted to the intensive care unit for monitoring and treatment with intravenous fluids and pressors. With use of vasoconstrictors such as epinephrine, gangrene of the digits and toes often develops (10). It is not clear whether this gangrene is due to the pressors, the GABHS infection, or both.

Most patients with streptococcal TSS have fulminating septicemia with severe multiple organ failure, frequently before shock develops. These events appear to be toxin-mediated, and by the time the diagnosis is suspected and treatment is initiated, the outcome may

already be determined, since streptococcal TSS has a 30-70% mortality rate (9,10,11). Complications of streptococcal TSS include shock (100%), acute respiratory distress syndrome (55%), renal impairment (80%), amputation (10%) and death (30%).

Questions

1. True/False: The prevalence of menstrual TSS has decreased markedly with the removal from the market of superabsorbent polyacrylate fiber tampons.
2. True/False: Vomiting, diarrhea, and abdominal pain are nearly ALWAYS seen in staphylococcal TSS but are rare in streptococcal TSS.
3. True/False: Oral mucosa hyperemia and hypertrophy of the tongue papillae are often seen in staphylococcal TSS but are seen in few patients with streptococcal TSS.
4. True/False: Blood cultures are usually positive in streptococcal TSS, but are usually negative in staphylococcal TSS.
5. True/False: Mortality for both staphylococcal and streptococcal TSS is about 50%.
6. True/False: In both staphylococcal and streptococcal TSS, desquamation of the hands and feet begins at about day 5-7, and is complete by day 10-12.
7. True/False: Multiorgan failure is usually present at the time of admission with streptococcal TSS, but appears later in the course with staphylococcal TSS.
8. True/False: Even though GABHS are sensitive to penicillin, the efficacy of penicillin may be reduced during overwhelming streptococcal sepsis due to the Eagle effect.
9. True/False: The prodrome of streptococcal TSS is very vague and may be associated with some seemingly unrelated minor trauma.
10. True/False: The source of staphylococcal TSS may be a superficial skin or mucocutaneous lesion which appears insignificant.

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Answers to questions

1. True
2. True
3. True
4. True
5. False. The mortality rate for Strep TSS is 30-70%. The mortality rate for Staph TSS is much lower.
6. True

7. True
8. True
9. True
10. True. Examples include impetigo and paronychia.

Chapter VI.19. Tuberculosis
Wallace J. Matthews, Jr., MD

La Boheme - Poverty and TB
La Traviata - Prostitution and TB
Long Days Journey Into Night - Foreign Born and TB
Moulin Rouge - Alternate Life Style and TB
And The Band Played On - AIDS and TB

A 2 year old girl is seen for irritability and fever. Her family had moved to Hawaii from the Marshall Islands 6 months ago. She had presented with anemia and malnutrition at the age of 9 months and her PPD (purified protein derivative) skin test had 17 mm of induration at 48 hours. Her chest film showed increased markings but no cavitary lesions. The radiologist was not certain if hilar adenopathy was present. She was treated with INH for 3 months and was scheduled to continue receiving INH therapy twice weekly but was lost to follow-up.

She is not as alert as usual and has a stiff neck. Her present chest film shows hilar adenopathy with multiple small lesions throughout all lung fields. A head CAT scan demonstrates enlarged lateral ventricles, enhancement of the meninges at the base of the brain and small vessel brain stem infarcts with possible pons involvement. There are no suggestions of significantly increased intra-cranial pressure. A lumbar puncture is performed. The opening pressure is 21 cm, white cell count 525, 85% lymphs, protein 86, glucose 55 (blood glucose 92). Cultures are sent which later grow Mycobacterium tuberculosis.

Known as "consumption", the white plague, and the white death, tuberculosis is perhaps the earliest, documented bacterial disease of humanity. Because of its characteristic pulmonary scarring and bony changes, it has been documented in human remains as ancient and diverse as the Egyptian and Incan mummies to the sand preserved natural remains found in the Chinese deserts of Asia Minor.

In the late part of the 19th and early part of the 20th century, almost all adults showed evidence of exposure and immune response to Mycobacterium tuberculosis. The recognition of TB as a major health issue is even becoming known in the popular press. In a special on War on Disease, National Geographic reported that one third of humanity are now carriers of tuberculosis (1). TB exposure was determined by a positive OT (old tuberculin) skin test. Skin testing by PPD (purified protein derivative) is now the standard (available since the 1930s) (1,2).

In the United States in general, and Hawaii in specific, there has been a rapid decrease in tuberculosis because of dramatic improvement in the living conditions of city dwellers (sociologic), the recognition of the means of spread the disease (epidemiological), isolation of contagious individuals in sanatoriums, as well as the development of anti-tuberculosis chemotherapy (bacteriologic and anti-microbial). There has been a 9-fold decrease in reported TB cases in Hawaii from 1060 cases in 1930 to 136 cases in 2000. This is in spite of a dramatic increase in population over that same time span. Indeed, tuberculosis was considered a vanishing disease and the medical specialists in this field and the public health resources spent on it were vanishing as well. It was thought of as a residual third world problem.

Hawaii has always had rates of infection much higher than the rest of the country. The case rate of TB in Hawaii is now about 2 times the national average 11.2 vs. 5.8 cases per 100,000 population (4). It is also clear that most newly diagnosed cases are imported and occur in foreign-born individuals (4). The spike in cases in 1992 was due to World War II Philippine veterans being required to come to the US to register for veteran benefits and having their TB recognized while here. Foreign born TB cases in Hawaii account for 83% of all cases as compared to 46% of cases on the mainland (1). In Hawaii, these are patients are from Southeast Asia and the West Pacific Islands. Patients from the Philippines account for 63% of TB cases while native born cases account for only 16%. Pacific Island immigrants from COFA (Compact of Free Association) (former trust Territories, Republic of Marshall Islands, Federated States of Micronesia, Palau) made up 44% of the cases from 1995-2000. In the rest of the United States, TB is also found among foreign born, but these individuals are from Mexico and South America in addition to Asia (5). The length of residence in Hawaii at the time of a TB diagnosis was <1 year whereas on the mainland it occurred somewhat later at 1-5 years of residency (6). From these data, the highest risk individuals are foreign born and are diagnosed soon after coming to Hawaii.

The diagnosis of TB depends upon clinical suspicion, isolation of the organism or its specific DNA, the tuberculosis skin test (PPD) or the response to therapy. It can involve any organ, can range from having no symptoms to overwhelming symptoms, progress indolently or become rapidly fatal, can be local or systemic. These facts make it clear that the slogan "Think TB" is correct, especially here in Hawaii.

The TB skin test is the only available standardized method for identifying latent TB infection. It consists of injecting 0.1ml of intermediate PPD (5 TU) intracutaneously into the volar surface of the forearm. It is to be read at 48-72 hours although a positive result can be read up to 7 days after testing. It must be read by a trained health professional. Self-reading is not allowed. Induration, not erythema, is measured in millimeters. The cutaneous reaction depends on an intact cellular immune response to the TB antigens. Tine or multiple puncture tests are no longer allowable. False positive tests do occur with other non-TB mycobacterium antigens. False negatives occur both with improper placement of the antigen as well as when immunity decreases or is interfered with by other disease. The Center for Disease control has suggested different cut off levels for different populations. Positivity is based on a statistical probability that a reaction reflects true Mycobacterium tuberculosis infection. A 5 mm test is considered positive in cases of close contact with a confirmed case, in patients with an abnormal chest film consistent with old or active TB, on immigration visa adjustment examination and in patients with HIV (a 5mm test might still be falsely negative in HIV patients with a CD4 count of less than 100). A 10 mm reaction is considered

positive in areas of high TB incidence such as Hawaii. It includes most TB positive patients with a relatively small number of false positives. In all other groups, a 15 mm test is considered positive. This higher level is especially useful in areas that have a high incidence of exposure to atypical Mycobacterium. A booster phenomena is known where the initial test is negative but reverts to its correct positive status with repeat testing in 1-4 weeks. Individuals who are truly negative will not boost. Repeated testing does not sensitize uninfected individuals. Anergy panel skin testing (testing for anergy) is no longer recommended. It was unreliable due to non-standardized antigens and did not seem to have clinical relevance.

BCG (Bacille Calmette-Guerin) vaccination is still used in some other countries. It is effective in preventing disseminated tuberculosis, especially tubercular meningitis in infants. Its efficacy in preventing pulmonary tuberculosis is debated. It is still used in countries with high rates of tuberculosis. It is also recommended as part of a treatment program for newborns of mothers with active pulmonary tuberculosis. It is a live vaccine derived from Mycobacterium bovis strains. The current recommendation is that individuals who have received BCG should have this fact ignored and their PPD tests interpreted the same as other individuals. The only exception is if the immunization was given less than 1 year previously.

Replacement tests for the PPD skin test have been sought to help with the difficulty of correct placement, having the patient return for a reading of the test, correct reading of the PPD and correct evaluation of these results. A newer test, Quantiferon, is a blood test that is in the final stages of FDA testing and will, in all likelihood, replace PPD testing. It recognizes Mycobacterium TB specifically and eliminates the cross-reactions in patient who have been exposed to atypical organisms as well as those who have received BCG immunizations.

Because of all of the problems noted above and because of the emergence of multiple drug resistant TB, it is very important to isolate the organism in suspected cases of tuberculosis. Children rarely produce sputum and this makes the isolation of organisms especially problematic.

Asymptomatic primary tuberculosis (7) is the most frequent clinical presentation in pediatrics. It is recognized during contact work-up or routine tuberculin testing. The child is asymptomatic. The chest film is usually normal but might have some hilar adenopathy. A 25 year study of TB in Baltimore documented the morbidity and mortality of non-treated, asymptomatic TB (8). For this reason, adults with asymptomatic TB are treated with INH for 6 months. The duration of therapy in children is longer than in adults. Converters are treated with INH for 9 months. This minimizes the occurrence of more progressive TB infections. In our case example, the positive PPD led to treatment as is appropriate but the therapy was discontinued. This results in the risk of drug resistance as well as subsequent disease as noted above.

Because treatment with INH for 9 months is associated with completion rates as low as 5-25% (9,10) shorter duration regimes have been advocated for latent TB including a 2 month schedule of rifampin and pyrazinamide. The reports of death from hepatitis associated with this regime have brought this practice into question (11). In addition, because of the compliance issues noted above, direct observed therapy has become more common.

Our patient might well have pulmonary tuberculosis. Pulmonary tuberculosis can be seen in children as well as adults. In adults, sputum smears are positive in 40-60% (i.e., organisms are identified on an acid fast stain of the sputum) of confirmed cases of pulmonary TB. Most cases of TB in adults have positive cultures or smears (82%). 96% of cases with cavitary pulmonary lesions on CXR will have a positive culture, as will 70% of cases with focal infiltrates. A positive smear requires 10,000 to 1,000,000 organisms/ml of sputum. In cavitary disease, the smears are usually positive and a negative smear strongly suggests another etiology. The culture, of course, is the gold standard for tuberculosis. Cultures are usually positive in 4-8 weeks although BACTEC liquid cultures may be positive in 2-4 weeks (12). In these studies, antibiotics to suppress all other growth are added and radiolabeled carbon-14 substrates are used. Radiolabeled carbon dioxide is measured as an indication of the presence of Mycobacterium tuberculosis.

Other technologies have the possibility of more rapid diagnosis for tuberculosis. Nucleic Acid Amplification Tests (NAATs) are available in 2 probes, Gen-Probe MTD and Roche Amplicor. Guidelines for the use of these tests as well as an algorithm are available (13). They are licensed for use on respiratory samples only and are limited to patients who have not been on anti-TB treatment for more than 7 days or who have been treated within the past 12 months. They do not replace cultures. In smear positive cases, they have a sensitivity of 95% and specificity of 98%. In smear negative cases, they have a sensitivity of 50% and a specificity of 95%. If cultures and NAATs are discordant, the cultures remain the gold standard. Additional means of obtaining specimens include fine needle aspiration, bronchoalveolar lavage or transbronchial biopsies. These tests are also useful to uncover a different diagnosis.

Since children do not produce sputum, isolation of the organism is much more difficult. Gastric washings may be used as a specimen source. Even after this, the organism may not be recovered. When all of these tests fail in a pediatric patient, a search should be undertaken for the organism from the person infecting the child. This organism, if found, can serve as a surrogate specimen for drug sensitivity testing.

Pleurisy with effusions, although rare in young children, may be seen in older children and is more common in boys than in girls. Its onset is rapid with signs of pneumonia. Fever is usually present and can last for weeks. Thoracentesis yields fluid with a low glucose, high protein and predominantly lymphocytic cells. Smears of the effusion are frequently negative for TB, as are cultures. Pleural biopsy, perhaps by a thorascope these days, increases the yield of both of these studies (7).

TB by diagnostic site shows that pulmonary makes up of 87% of cases, pleural 3%, lymphatic 6%, bone/joint <1%, genitourinary <1% and meningeal 2%. In pediatric patients, all of these infections are possible but the most likely are pulmonary TB and meningitis.

Our patient has confirmed tubercular meningitis. Note that the cell count is largely mononuclear/lymphocytic, similar to viral meningitis in this regard. The CAT scan noted above is virtually diagnostic. Isolation of the organism is crucial as in all cases of TB. Drug therapy is aimed at the isolated organism but until that occurs 4 or 5 drugs are used.

Multiple drug resistant TB is the major concern. Primary drug resistance to anti-TB medications occurs in nature. For INH, the rate of resistance is 1 in 1 million, for rifampin 1 in 100 million and for both INH and rifampin 1 in 100 trillion. Since cavitary lung lesions contain approximately 1 billion organisms, naturally occurring, primary resistance has not been a real problem. However, partially treated infections either due to inadequate length of therapy or lack of compliance, results in selecting multiple drug resistant TB organisms which is a major issue in treating TB patients and public health prevention programs. The standard treatment now consists of 4 drugs, INH and rifampin for 6 months and pyrazinamide and ethambutol for 2 months. Streptomycin can be substituted for ethambutol. Further treatment is based on cultures and sensitivity. In pediatric patients, treatment is more likely to be empiric. Some providers avoid ethambutol because of the difficult of monitoring for ethambutol associated optic neuritis. There have been no documented cases of optic neuritis in children. Because of this, many still use ethambutol.

Those with meningeal, bone or otherwise disseminated disease are treated for 12 or more months. All patients should receive directly observed therapy. In patients with confirmed drug resistance, changes in their regimes are required such that second and third line drugs are substituted (e.g., ethionamide, cycloserine, PAS, quinolones, clofazimine, amikacin, kanamycin, capreomycin). The length of treatment is also prolonged. These recommendations have changed frequently and it is best to get recommendations from the Department of Health or infectious disease experts.

The long-term consequences of TB meningitis are real and hydrocephalus and decreased functioning are almost universally seen.

TB requires vigilance both for the individual patient and the community. The rule is THINK TB.

Questions

1. True/False: Tuberculosis is a disease of the past and no longer a major health care issue.
2. True/False: Testing with PPD is a useful screening test for patients suspected of having tuberculosis.
3. True/False: A history of BCG vaccination makes PPD testing contraindicated and the results unreliable.
4. True/False: Children with a positive PPD skin test and a positive chest film should be treated with INH alone for 9 months.
5. True/False: The risk of multiple-drug resistant TB is much higher in patients that did not complete initial TB therapy.
6. True/False: Immigrants are at greater risk of having TB than native-born Americans.
7. True/False: Patients with HIV/AIDS have a higher rate of acquiring pulmonary TB than the general population.
8. True/False: Health care workers are at a greater risk of acquiring TB than the general population.
9. True/False: Ethambutol cannot be used in pediatric patients since vision testing is often impossible.
10. True/False: Hawaii has a lower rate of TB than the rest of the US.

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Answers to questions

1.F. 2.T, 3.F, 4.F, 5.T, 6.T, 7.T, 8.T, 9.F, 10.F

Chapter VI.20. Human Immunodeficiency Virus (HIV) Infections

Guliz Erdem, MD
Cecilia M. Shikuma, MD

An 18 year old student has a three week history of worsening headache, myalgias and fever not responding to acetaminophen (Case scenario is adapted from reference 1). His primary care physician diagnosed him to have a "viral syndrome". He was noted to have oral thrush and was advised to undergo HIV testing (which he did 10 days ago) because he admitted to being bisexual and engaging in unprotected sex. He also had a truncal rash and arthralgias 5 days previously (currently resolved). He denies illicit drug use.

Exam: VS T 39, P 118, RR 24, BP 110/74. He is mildly ill appearing. His head, ear, heart and lung exams are normal. His oral exam is significant for thrush. His abdomen is nontender, liver edge palpable 3 cm below the right costal margin (liver span 11 cm), moderate splenomegaly is present. Skin without rash. Small, nontender anterior/posterior cervical and occipital lymphadenopathies are present. No focal neurologic findings are present, but he has some meningeal signs.

Lab: CBC: WBC: 11,500, 93% neutrophils, 3% lymphocytes, 1% monocytes, 3% atypical lymphocytes, Hct 45. Serum transaminases slightly elevated. Heterophil antibody (Monospot) negative. Serum RPR negative. HIV ELISA (performed 10 days earlier) was negative. A lumbar puncture is performed. CSF analysis shows 22 WBC, 95% lymphocytes and 5% PMNs. The CSF protein is mildly elevated. CSF VDRL is negative.

His symptoms gradually improve after initiation of treatment with several antiretroviral medications. You thought that this patient is recently infected with HIV and his symptoms are consistent with HIV aseptic meningitis and a mononucleosis like syndrome. This phenomenon is also called acute retroviral syndrome and occurs 2-8 weeks after exposure. The HIV ELISA tests can be initially negative as it was in this patient. The decrease in the absolute lymphocyte count and increase in serum transaminases are common. CSF lymphocytic pleocytosis can be seen at any stage of HIV disease. CSF pleocytosis diminishes and protein elevation persists as HIV disease advances. The finding of pleocytosis in advanced disease warrants exclusion of other etiologies.

Since AIDS was recognized as a distinct disease in 1981, over 50 million individuals worldwide have been infected by HIV-1 (2). An estimated 1.3 million children under 15 are living with HIV/AIDS. As of January 1, 2000, 8718 cases of AIDS in children <13 years old had been reported, and approximately 60% of these children have died (3).

HIV is transmitted by both homosexual and heterosexual contact, by blood and blood products, by infected mothers to infants either intrapartum, perinatally or via breast milk. Heterosexual transmission is the most common mode of infection worldwide. The presence of other sexually transmitted diseases in the partners increases the risk of transmission. The risk of HIV transmission following skin puncture from a needle that was contaminated with blood from a patient with HIV infection depends on multiple factors (such as the viral load of the patient, the amount of the blood on the needle, etc.) and without antiretroviral therapy, the transmission risk is about 0.3%.

Women, in whom HIV infection is most often acquired via heterosexual sex, now comprise the group in which HIV infection is increasing most rapidly in the United States. About 25% of the infants born to HIV-seropositive mothers who are not receiving antiretroviral therapy are infected by HIV-1 (4,5). Perinatal transmission can occur during pregnancy, during labor and delivery and after delivery through breast-feeding. In the absence of breast feeding, 60-75% of transmission occurs during labor and delivery. Among women who breast feed, breast feeding is responsible for 10-15% of transmission. Clinical factors that increase the likelihood of perinatal transmission include immunologically or clinically advanced HIV disease in the mother, high plasma viral load, maternal injection drug use during pregnancy, preterm delivery, non-receipt of antiretroviral treatment and breast-feeding. Obstetric factors are also important. Delivery >4 hours after the rupture of fetal membranes can double the risk of transmission. Chorioamnionitis and maternal infection with another sexually transmitted disease during pregnancy increase the risk. Most of these risk factors have been identified before the use of zidovudine chemoprophylaxis and their effects are unknown now, since most pregnant infected women are receiving treatment. Reducing the exposure of the infant to the maternal blood and secretions during the intrapartum period as in cesarean section can prevent HIV transmission. The birth of every perinatally HIV-infected infant signals either a missed prevention opportunity (no prenatal care, HIV testing is not offered or obtained, no prophylaxis) or, more rarely, a failure of prophylaxis.

The term HIV syndrome is used to describe the cellular and humoral immunodeficiency and the numerous complications that result from the HIV-1 and HIV-2 infections. Acquired immunodeficiency syndrome (AIDS) is the spectrum of disorders (HIV-wasting, opportunistic infections, certain malignancies) resulting from advanced HIV infection.

Also, any HIV-infected child with less than 15% of circulating lymphocytes as CD4+ T-lymphocytes (CD4 cell) has severe suppression regardless of the presence of symptoms or opportunistic infections. The CD4 cell counts may differ in children depending on their age and accordingly, the definitions for the immunosuppression level may differ between different age groups.

Etiology and establishment of infection

HIV is a RNA virus whose hallmark is the reverse transcription of its genomic RNA to DNA by the enzyme reverse transcriptase. HIV belongs to the family of human retroviruses and the subfamily of the lentiviruses. The four recognized human retroviruses belong to two distinct groups as the human T-lymphotropic viruses (HTLV-1 and HTLV-II) and the human immunodeficiency viruses (HIV-1 and HIV-2). HIV-2 was originally confined to West Africa, but a number of cases have been recently identified in other parts of the world.

The HIV viral envelope proteins (such as gp120 protein) have a high affinity (tropism) for the CD4 lymphocytes. In order for HIV to fuse to and enter its target cell (mostly CD4 cells), it must also bind to one of a group of co-receptors. The two major co-receptors are CCR5 and CXCR4. Both of these receptors belong to the family of G protein-coupled cellular receptors, and the use of one or the other or both receptors by the virus is an important determinant of the cellular tropism of the virus.

After HIV binds to CD4 cells, the viral and cellular membranes fuse via the gp41 molecule and the HIV nucleoprotein complex enters the cytoplasm. The RNA viral genome then undergoes transcription by the virally encoded reverse transcriptase. The double stranded viral DNA enters into the nucleus, where integration of the DNA provirus into the host chromosome is catalyzed by the enzyme "integrase". This provirus may remain transcriptionally inactive (latent) or it may manifest varying levels of gene expression.

When a CD4 cell with the integrated provirus is activated, the viral particles are assembled and virions are released from the cell by budding. Productive viral replication is lytic to the infected T cells. Rapid production and turnover of CD4 cells occur throughout the course of HIV infection. Although a highly dynamic, complex equilibrium between HIV and CD4+ cells may be maintained for several years, eventually a decline in circulating CD4 cells occurs. A decrease in function as well as number of CD4 cells is central to the immune dysfunction in HIV infection.

The events associated with primary HIV infection are likely critical determinants of the subsequent course of HIV disease. In particular, the dissemination of the virus to lymphoid organs is a major factor in the establishment of a chronic and persistent infection. It is uncertain which cell in the blood or lymphoid tissue is the first to actually become infected; however, studies in animal models suggest that dendritic lineage cells may be the initial cells infected. These cells pass the virus on to CD4 cells in the draining lymph nodes of the animals. In humans this mechanism probably operates when the virus enters "locally" (such as vagina, rectum, upper gastrointestinal tract and breast milk) as opposed to directly into the blood.

In primary infection, virus replication in CD4 cells intensifies prior to the initiation of a virus specific immune response, leading to a burst of viremia and then to a rapid dissemination of the virus to other lymphoid organs, brain and other tissues. Two to eight weeks after initial exposure, up to 70% of the patients experience this immune response as a mononucleosis-like syndrome. These acute symptoms may last 3 days to 3 weeks and can include arthralgias, fever, headache, lymph node enlargement, maculopapular rash and sore throat. Ten percent to 20% of patients have neurologic involvement, usually presenting as aseptic meningitis with possible cerebrospinal fluid pleocytosis. The progression of diseases varies greatly among individuals and the route of HIV transmission does not influence the rate of progression. Generalized lymph node enlargement occurs in 35 to 60% of asymptomatic HIV-infected persons.

Despite the initial immune response, once infection is established, the virus is virtually never cleared from the body. A median of approximately 10 years passes before the patient becomes clinically ill. This period is shorter in perinatally infected children. HIV successfully evades elimination by the immune system in order to establish chronicity and the mechanisms of this evasion are not clear. This goes along with the establishment of a pool of latently infected, resting CD4 cells. These cells can remain in this state until an activation signal drives the expression of the replicating virus. This persistent pool of cells is a major obstacle to any goal of eradication of virus from the infected patients. Some degree of viremia is present in all untreated patients and the level of this "steady-state" viremia, called the "viral set point", at approximately 1 year has important prognostic implications. If the patients have a lower set point, it can be said that the disease progression will be much slower. Several genetic mutations can be responsible for this delay in the progression of the disease (as in certain deletions of the CCR5 co-receptor gene).

Diagnosis

In most centers, enzyme-linked immunosorbent assay (ELISA) is used as the primary screening test. If the test is reactive, it is repeated in duplicate and if either or both repeat tests are reactive, the sample is considered positive and a western blot or indirect immunofluorescence assay is done on the sample for confirmation. The western blot detects antibodies to specific denatured HIV-1 proteins. The absence of all bands in western blot is considered a negative test.

This protocol has a 3-4 week "window period" prior to seroconversion, during which results can be negative or indeterminate. Most experts suggest the use of plasma viral load (PVL) for patients that may be in the window period (as in the case scenario). In addition to PVL, very sensitive virological assays (RT-PCR, bDNA) are also used for diagnosis. However, one frequent consequence of using highly sensitive tests will be the loss of specificity, meaning that false-positive results will occur. For this reason, ELISA with a confirmatory western blot remains the "gold standard" for the diagnosis of infection in adults and older children. Rapid tests for expedited screening can be used in selected patients such as pregnant women.

The diagnosis of HIV infection in newborns and infants <18 months of age is different. Nearly all infants born to infected mothers passively acquire maternal antibodies and in some instances will test positive regardless of whether they are infected. Definitive diagnosis in this age group requires virological tests as PCR or viral culture. Two positive assays on two separate specimens are required for diagnosis. Infant HIV testing should be done as soon possible. The infant who has two negative virological tests, both of which are performed at 1 month of age or older and one of which is performed at 4 months of age or older, is considered to have had HIV infection reasonably excluded in the absence of any clinical illness.

T cell counts are important for the diagnosis and laboratory monitoring of the patients. Generally, along with a decrease in the CD4+ levels, an increase in CD8+ levels is observed. This decrease in CD4+ to CD8+ ratio can also occur with other viral infections, such as those caused by CMV or EBV. CD4 count is generally accepted as the best indicator of the immediate state of immunologic competence of the patient.

Response of T-lymphocytes to plant lectin mitogens (pokeweed) are decreased or absent and patients may be anergic to skin tests. Serum immunoglobulins, particularly IgG and IgA are frequently elevated during the early stages of HIV infection.

Clinical manifestations

The clinical manifestations can be due to HIV or its complications. The disease spectrum changes from primary infection with or without the acute syndrome to the asymptomatic stage and to advanced disease. Approximately 50% of untreated patients develop AIDS within 10 years. An additional 30% will have mild symptoms of immunodeficiency and fewer than 20% will be entirely asymptomatic.

The pediatric manifestations usually include generalized lymphadenopathy, hepatomegaly, splenomegaly, failure to thrive, oral candidiasis, recurrent diarrhea, parotitis, cardiomyopathy, hepatitis, nephropathy, CNS disease (including developmental delay), lymphoid interstitial pneumonia, recurrent invasive bacterial infections, opportunistic infections and malignancies. Fever is common and can be due to Mycobacterium avium complex, toxoplasmosis, CMV infection, tuberculosis, Pneumocystis carinii infection, salmonellosis, cryptococcosis, histoplasmosis, medications or malignancies. Acute bronchitis and sinusitis are more prevalent during all stages of disease. The most common causes of pneumonia are the bacterial infections and Pneumocystis carinii pneumonia (PCP). PCP occurs most frequently in infants between 3 and 6 months of age who acquire infection before at birth. In addition to these pulmonary manifestations, another important clinical feature in children is lymphoid interstitial pneumonitis (LIP). LIP is a benign lung infiltrate and is felt to be part of the polyclonal activation of lymphocytes. It is generally self-limited and no specific treatment is necessary. HIV infected patients appear to be particularly prone to infections with encapsulated microorganisms such as S. pneumoniae and H. influenzae type B.

Malignancies in pediatric HIV infection have been relatively uncommon, but leiomyosarcomas, CNS lymphomas, and Burkitt lymphomas occur much more frequently in children with HIV infection than in nonimmunocompromised children. The development of opportunistic infections, particularly PCP, progressive neurologic disease, and severe wasting is associated with a poor prognosis.

HIV pediatric findings have been revised into 4 categories (4):

Category N: Not symptomatic. These children may have only one of the conditions from category A. These patients have CD4 cells >25%.

Category A: Mildly symptomatic. They can have 2 or more of the following conditions: lymphadenopathy, hepatomegaly, splenomegaly, dermatitis, parotitis, recurrent or persistent upper respiratory tract infections.

Category B: Moderately symptomatic. Findings may include but are not limited to: anemia, neutropenia, single episode of meningitis, pneumonia, recurrent or chronic diarrhea, HSV infections, lymphoid interstitial pneumonitis, persistent fever (>1 month). Category C: Any condition listed as "AIDS defining conditions" including serious multiple and recurrent bacterial infections, candidiasis, disseminated coccidioidomycosis and histoplasmosis, extrapulmonary cryptococcosis, cryptosporidiosis >1 month, CMV infection developing after 1 month of age. It also includes wasting syndrome (persistent weight loss >10% of baseline or downward crossing of at least 2 of the following percentile lines on the weight for age chart in a child >1 year of age or <5th percentile on weight for height chart on 2 consecutive measurements plus chronic diarrhea or documented fever), encephalopathy, Kaposi's sarcoma, lymphomas. These patients usually have circulating CD4 cells of <15%.

Treatment

Initiation of antiretroviral treatment (ART) depends upon virologic, immunologic and clinical criteria. The CD4+ lymphocyte count or percentage value is used in conjunction with viral load to guide treatment decisions and primary prophylaxis of PCP after age 1 year. Expert opinions and knowledge about diagnostic and therapeutic strategies are changing rapidly and these can be followed from several resources such as: www.hivatis.org (posts federally approved treatment guidelines), www.actis.org (information on federally funded and privately funded clinical trials), www.cdcnpin.org (updates on epidemiologic data from the CDC), www.cc.nih.gov/hiv-mgt (online images of HIV drugs and information regarding dosing). If enrollment into clinical trials is possible, enrollment of the HIV-infected child into an available clinical trial should be encouraged. There are several groups of drugs used in ART.

Nucleoside analog reverse transcriptase inhibitors (NRTIs): zidovudine (ZDV-Retrovir), didanosine (ddI-Videx), lamivudine (3TC, Epivir), stavudine (d4T, Zerit), zalcitabine (ddC, Hivid), abacavir (ABC, Ziagen).

Non-nucleoside analog reverse transcriptase inhibitors (NNRTIs): nevirapine (NVP, Viramune), efavirenz (EFV, DMP-266, Sustiva).

Protease inhibitors (PIs): ritonavir (Norvir), indinavir (Crixivan), nelfinavir (Viracept), saquinavir (Invirase, Fortovase), amprenavir (Agenerase), ABT-378/r (Kaletra).

Fusion inhibitors: T-20.

Antiretroviral therapy has provided substantial clinical benefits to HIV-infected children with immunologic or clinical symptoms of HIV infection. Studies have demonstrated substantial improvements in neurodevelopment, growth, and immunologic and/or virologic status with initiation of ZDV, ddI, 3TC, or stavudine monotherapy . More recent pediatric trials of symptomatic children who have not previously received antiretrovirals have demonstrated that combination therapy with either ZDV and 3TC or ZDV and ddI is clinically, immunologically, and virologically superior to monotherapy. When compared with monotherapy, combination therapy: a) slows disease progression and improves survival, b) results in a greater and more sustained virologic response and c) delays development of virus mutations resistant to the drugs being used. Data from clinical trials that address the effectiveness of antiretroviral therapy in asymptomatic infants and children with normal immune function are not available. However, initiation of therapy early in the course of HIV infection, including during the period of primary infection in the neonate, is theoretically advantageous. Antiretroviral treatment is definitely required in the presence of any AIDS-definitive infection (Category C), wasting or failure to thrive, HIV encephalopathy, AIDS-associated malignancy and two episodes of meningitis or sepsis. Several ART drugs are not approved for use in children. ART should be initiated by a pediatric infectious diseases specialist with expertise in HIV infection and its treatment. Generally, the combination of a protease inhibitor and two non-nucleoside RTIs is recommended for initial antiretroviral therapy. If the patients cannot swallow pills, the PIs nelfinavir or ritonavir can be used. If they can swallow pills, indinavir can also be used. Another recommended alternative to this treatment is nevirapine with two NRTIs or abacavir with ZDV and 3TC. Monotherapy, d4T/ZDV, ddC/ddI, ddC/d4T, ddC/3TC treatments are not generally recommended.

Adherence to treatment can be increased by use of suitable formulations, use of G-tubes, and directly observed therapy. Drug concentrations should be monitored. Viral assays can be done to assess resistance. ART may have serious side effects and patients should be carefully monitored. There are currently no data available that define the threshold at which a change in therapy should occur. If the PVL is above detectable limits on two determinations or if the PVL exceeds the arbitrary figure of 10,000 to 20,000 copies/mL, a change in therapy may be considered. PVL assays and CD4 cell counts should be repeated at 3 to 4 month intervals during therapy.

Early diagnosis and aggressive treatment of opportunistic infections may prolong survival. Four major opportunistic infections need to be considered for prophylactic treatment: bacteremia/sepsis, Pneumocystis carinii infection (PCP), tuberculosis and mycobacterium avium/m. intracellulare infection. For infants younger than 1 year of age with possible or proven HIV infection, PCP prophylaxis should be administered at 4 to 6 weeks of age and continued for the first year of life unless infection is excluded.

IVIG can be given in addition to ART to children with hypogammaglobulinemia, recurrent, serious bacterial infections, children who fail to develop antibodies to common antigens and to children living in areas where measles is highly prevalent who have not developed an antibody response after two doses of MMR.

Treatment of HIV-infected women with zidovudine during the second and third trimester of pregnancy and during delivery, followed by zidovudine treatment of the infant for 6 weeks is shown to decrease maternal-fetal transmission to 8%.

Following significant exposure of health care employees (needle-stick injuries) prompt administration of a combination regimen of indinavir, zidovudine, and lamivudine, significantly decreases the likelihood of HIV infection.

Immunizations

In general, live virus (OPV) vaccines and live bacterial (BCG) vaccines should not be given to patients with AIDS or other clinical manifestations of HIV infection indicative of significant immunosuppression. An exception is MMR vaccine which can be given to patients who are not severely immunocompromised. Other routinely recommended vaccines, should be given according to the usual immunization schedule. Pneumococcal vaccine and influenza vaccination are also recommended. Varicella vaccine can be administered to asymptomatic patients if the benefits of vaccination outweigh its risks.

Control measures

In addition to the measures for the reduction of perinatal HIV transmission and counseling of HIV-infected women to not breastfeed; education, counseling, behavior modification are the cornerstones of infection prevention. Another important point is that HIV infected children should not be excluded from day-care centers or schools for the protection of other children or personnel. The need for a more restricted environment should be evaluated on a case by case basis with consideration of conditions that may pose an increased risk to others, such as aggressive biting behavior or the presence of exudative, weeping skin lesions that cannot be covered. Only the child's parents, guardians, and physician have an absolute need to know that the child is HIV infected. The number of personnel aware of the child's condition should be kept to the minimum needed to ensure proper care of the child.

HIV vaccines using viral surface proteins, non-HIV live vector viruses, combination of several viral elements, naked DNA and HIV protein fragments are studied and in some instances clinical trials are being performed.

Questions

1. Which one of the following is not a finding in HIV wasting syndrome?
   a. <5th percentile on weight-for-height chart on 2 consecutive measurements.
   b. Chronic diarrhea.
   c. Temperature of 38.5 °C, intermittently during the last 2 months.
   d. Persistent weight loss.
   e. Thrombocytopenia.

2. Which one of the following is used as a screening test in HIV infection diagnosis?
   a. Enzyme immunoassay
   b. Polymerase chain reaction
   c. Western-blot
   d. Immune fluorescence assay
   e. Viral culture

3. Which of the following vaccines is not routinely recommended in HIV infected asymptomatic children?
   a. IPV
   b. MMR
   c. Hib
   d. Pneumococcal
   e. Varicella

4. Which of the following is a definite indication to start antiretroviral treatment in HIV infected children?
   a. CD4 cell counts >1500 in a 4 year old asymptomatic child.
   b. Pneumocystis carinii pneumonia.
   c. Recurrent otitis media but no other symptoms.
   d. Bilateral anterior cervical lymphadenopathy.

5. Which one of the following is/are not shown to be a transmission route for HIV infection?
   a. Vertical transmission
   b. Breast feeding
   c. Vectors
   d. Blood transfusion
   e. Heterosexual sex

6. Which of the following enzymes have critical importance in the establishment of HIV infection?
   a. Neuraminidase
   b. DNA polymerase
   c. Protein kinase
   d. RNA polymerase
   e. Reverse transcriptase

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Answers to questions

1.e, 2.a, 3.e, 4.b, 5.c, 6.e

Chapter VI.21. Sexually Transmitted Infections
Reina M. Ahern, MD

This is a 17 year old female who presents to the ER with a chief complaint of abdominal pain and vaginal discharge. She noticed a yellow-green vaginal discharge approximately three days prior, with cramping. She is experiencing worsening lower abdominal pain beginning yesterday, which is now 5/10 in intensity. She is having some nausea, but no vomiting or changes in bowel movements. LMP was two weeks ago. She recently began dating a college senior whom she met at a university party 4 months ago. She admits to having unprotected sex with him three times in the last month. She also recalls that he had some burning with urination a few days ago. Her past surgical history is significant for a previous ITOP (intentional termination of pregnancy) at age 16. Otherwise, she does not have any medical problems or take any medications.

Exam: VS T 38.7, P 95, R 20, BP 130/86. HEENT, neck, cardiac, and lung exams are unremarkable. Abdominal exam is significant for mild right upper quadrant tenderness and moderately severe lower abdominal (pelvic region) tenderness. Pelvic exam reveals mucopurulent vaginal discharge, right adnexal tenderness, and severe cervical motion tenderness. A urine sample tests negative for beta-hCG and it is sent for a DNA amplification assay for Chlamydia. A cervical swab and gram stain of the vaginal discharge demonstrates many WBCs and multiple intracellular gram negative cocci. Transvaginal ultrasound shows thick, fluid filled fallopian tubes with free fluid in the cul-de-sac. She is hospitalized and treated with IV cefotetan and oral doxycycline.

Sexually transmitted infections (STI), also known as sexually transmitted diseases (STDs), are a significant cause of morbidity and mortality in the world, particularly in adolescents who are prone to adopting high-risk behaviors. Epidemiologic studies show teenagers initiating sexual activity earlier than before, with nearly half of all adolescents sexually active by age 17 (1). Adolescents who initiate sexual intercourse at younger ages are more likely to have multiple partners, thus increasing their chances of becoming infected. Experimentation with alcohol and drugs may compromise an adolescent's ability to make sound judgments about sex and contraception. Those particularly at risk for STIs include homosexual males, street youth, incarcerated adolescents, teens engaged in prostitution, and injection drug users (1,2). Adolescents, in particular, face obstacles in utilizing health care services. Embarrassment about discussing sexuality with health care providers may discourage adolescents from seeking care. Limited financial independence and transportation barriers for teenagers may also reduce access to health care. Consequently, the incidence of STIs among adolescents is increasing with 3 million American teenagers infected each year (3). These numbers are difficult to estimate accurately, but suffice it to say, that STIs are common and a major health care concern.

Primary prevention of STIs is the chief goal for health care providers, with emphasis on safe sexual practices or abstinence. When condoms are used correctly and consistently, they are highly effective in preventing spread of STIs. However, condoms may not provide complete protection against human papillomavirus, herpesvirus type 2, and C. trachomatis (3). As younger adolescents engage in high-risk sexual activity, early recognition of the various clinical syndromes may further decrease the long-term health consequences associated with STIs. The number of identified STIs has increased to more than 20 pathogens, 8 of which have been newly recognized since 1980 (1,3). Fortunately, there is a limited set of clinical presentations. Genital ulcers occur with both Treponema pallidum (syphilis) and herpes simplex type 2 (genital herpes), as well as the rarer Haemophilus ducreyi (chancroid) and Calymmatobacterium granulomatis (granuloma inguinale). Certain serotypes of human papillomavirus cause nonulcerative genital warts (condyloma acuminata). Pubic lice, caused by Phthirus pubis, manifest as pruritus and may demonstrate eggs at the base of pubic hairs. Vaginal discharge may be noted with Candida albicans (vulvovaginal candidiasis, white cottage cheese discharge) and Gardnerella vaginalis (bacterial vaginosis, fishy foul odor), which are not considered to be sexually transmitted, but also with Trichomonas vaginalis (trichomoniasis), which is. Urethritis in the male and cervicitis or PID in the female can result from infection with Neisseria gonorrhoeae (gonorrhea) and/or Chlamydia trachomatis (chlamydia) (2). The Centers for Disease Control and Prevention (CDC) also require physicians in every state to report syphilis, gonorrhea, chlamydia, and AIDS.

STIs with serious long-term sequelae include: 1) human papillomavirus (HPV) infection, which leads to an increased prevalence of cervical neoplasia in adolescents and cervical cancer in adults; 2) chlamydia and 3) gonorrhea, which are the leading causes of pelvic inflammatory disease, tubal infertility, and infant pneumonia; 4) herpes simplex, which can result in recurrent painful episodes and subsequent neonatal infection; and 5) syphilis, which can be passed to offspring, resulting in congenital syphilis (1).

Of note, STIs diagnosed in preadolescent children (beyond the neonatal period) suggests sexual abuse. Acquisition of HIV, gonorrhea, chlamydia, and syphilis in the post-neonatal period is almost indisputably indicative of sexual contact (2). Other diseases are not as clearly connected, but sexual abuse should be suspected in infants and prepubertal children with trichomoniasis, genital herpes, and condyloma acuminata. Findings should be confirmed, and evidence should be reported to the appropriate community agency for child abuse or neglect (2).

Human Papillomavirus (HPV)

Papillomaviruses are members of the papovavirus family. They are non-enveloped, have an icosahedral virion capsid, and contain a double-stranded DNA genome. It is postulated that the virus gains entry into the body through microscopic abrasions of the surface epithelium, leading to transformation of basal cells. The natural history of HPV infection ranges from spontaneous regression to persistent infection and/or neoplastic progression (4). HPV transmission is very common, perhaps the most common sexually transmitted infection among young, sexually active people in the United States (5,6). There are multiple subtypes, e.g., subtypes 6 and 11 cause 90% of genital warts (condyloma acuminata). Nearly all cases of cervical cancer or squamous intraepithelial neoplasia are associated with HPV, particularly subtypes 16, 18, 31, 33, and 35 (5).

HPV produces subclinical infection in 70% of cases and overt infection in 30% (4). Condyloma acuminata or genital warts are the most widely recognized manifestation of HPV infection, often described as cauliflower-like in gross appearance. The most common sites of these lesions are the posterior fourchette, adjacent labia and perineum, introitus, vagina, and cervix (4). Depending on the size and location, genital warts can be painful, friable, and pruritic (2). Conversely, cervical intraepithelial dysplasia is asymptomatic, but can be detected by a Pap smear.

Traditionally, the diagnosis of HPV in sexually active adolescents is made by visual inspection, often with colposcopy. Tissue infected with HPV often undergoes epithelial hyperplasia and has a shiny white appearance (acetowhitening) after being soaked with acetic acid (4). Biopsy of lesions can be sent for light microscopy or DNA subtyping (4). The use of DNA testing of vaginal swabs to detect HPV in high risk individuals is being evaluated in screening for cervical cancer (5). Cytology of cervical scrapings (Pap smear)

permits the detection of cervical neoplasia, widely believed to be triggered by certain serotypes of HPV. However, screening with the Pap smear results in a significant number of false negatives. For patients who have a Pap test indicative of low-grade SIL (squamous intraepithelial lesion) or ASCUS (atypical squamous cells of undetermined significance), follow-up with repeat Pap tests every 6 months for 2 years may be acceptable without colposcopy. If repeat tests show persistent abnormalities or if compliance is an issue, colposcopy and directed biopsy may be indicated (2).

HPV spontaneously resolves in many patients (4). Therefore, the goal of therapy should target symptomatic manifestations. In general, there are patient-applied and provider-applied modalities of treatment. Patients may apply podofilox solution or gel or imiquimod cream to visible lesions. Alternatively, condyloma can be managed by topical application of trichloroacetic acid (TCA), cryotherapy, or podophyllin by a health professional. Surgical removal is indicated if topical therapy fails, for extensive lesions, or for a young patient who requires general anesthesia (4). No clear evidence exists to determine whether treatment of genital warts will reduce transmission (2). All adolescent women with anogenital warts should have a Pap smear, with follow-up recommended every 6 months (4).

Chlamydia

C. trachomatis is an obligate intracellular organism that does not gram stain. Infected cells contain cytoplasmic Giemsa stain-positive inclusions. C. trachomatis has at least 15 different immunotypes. Types D through K are responsible for the majority of genital infections, including mucopurulent cervicitis, urethritis, proctitis, epididymitis, salpingitis, endometritis, and perihepatitis. Types L1 through L3 are associated with lymphogranuloma venereum. Ocular trachoma (a chronic follicular keratoconjunctivitis which is a common cause of acquired blindness in other countries), is caused by types A-C (4).

Chlamydia is one of the most prevalent bacterial STIs in the United States, accounting for an estimated 3-4 million new cases each year, more frequently diagnosed in adolescents than gonorrhea (4,6). Up to 85% of women and 40% of men who are infected with chlamydia are asymptomatic (3). Yet if recognition and treatment are inadequate, pelvic inflammatory disease (PID) will develop in 20-40% of women with chlamydia (3). As with some other inflammatory STIs, transmission of HIV can be facilitated by chlamydial infection.

C. trachomatis infects the endocervix most often, in addition to the urethra, anus, Bartholin's glands, and fallopian tubes. The most common signs of C. trachomatis cervicitis include yellow/green mucopurulent endocervical discharge and an edematous, friable cervix (hypertrophic ectropion) which may present with abnormal vaginal bleeding (4). A wet-mount or gram stain of the discharge usually reveals greater than 30 polymorphonucleocytes (PMN) per high power field and absence of gonococci (although the presence of gonorrhea does not rule out concurrent chlamydia infection). Chlamydia urethritis should be suspected in sexually active females with prolonged dysuria (greater than 7-10 days) unresponsive to traditional treatment for bacterial cystitis (J). In males, chlamydial infection can also cause non-gonococcal urethritis, acute epididymitis, or proctitis. Chlamydial pharyngitis or conjunctivitis can occur in both males and females.

Chlamydia is diagnosed by cervical culture, antigen detection techniques (e.g., enzyme immunoassay, direct fluorescent antibody test), or DNA based testing (e.g., nucleic acid hybridization probe, DNA amplification). Although cervical culture for chlamydia is costly and technically difficult (it requires cell media culture because it is an obligate intracellular organism similar to a virus), it remains the gold standard and the procedure against which new diagnostic methods are measured (4). Tests for detecting chlamydial antigen have a sensitivity of approximately 60-80% (7). DNA amplification tests are the most recent development, including polymerase chain reaction (PCR) and ligase chain reaction (LCR). Both PCR and LCR are highly sensitive and specific with endocervical, urethral, and urine specimens from men and women (5,7,8). The U.S. Preventive Services Task Force strongly recommends that "all sexually active women 25 years and younger and other asymptomatic women at increased risk of infection" be routinely screened for chlamydial infection. This was based on evidence that screening women at risk reduces the incidence of PID (9). Urine-based home testing for chlamydia is expected to increase availability of low-cost screening (7). Shafer et al. reported that urine-based LCR screening, rather than routine pelvic examinations, was the most cost-effective strategy in asymptomatic sexually active adolescent girls because of greater acceptance of urine testing (10).

A single dose of azithromycin (1 gram) has been shown to be equally effective in treating chlamydia but at a modestly greater cost than a 7-day course of doxycycline (100 mg BID) (5). Azithromycin is an alternative regimen for pregnant women or patients for whom compliance is an issue (2). Either regimen is recommended for children older than 8 years of age (2). Patients should be encouraged to refer their sexual partners for diagnosis and treatment to prevent reinfection (2). A test of cure should be performed approximately 6 weeks after completion of treatment (7).

Pelvic inflammatory disease (PID) results from ascension of infection from the endocervix to the upper genital tract (e.g., endometritis, salpingitis). This is suggested by the triad of: 1) abdominal pain, 2) uterine/adnexal tenderness on bimanual exam, and 3) cervical motion tenderness. Symptoms often begin a few days after menstruation. Empiric treatment should be initiated if no other cause for these symptoms can be identified. Other findings that support the diagnosis (2) include: fever, abnormal cervical/vaginal mucopurulent discharge, presence of WBCs on saline microscopy of vaginal secretions, elevated acute phase reactants (WBC, ESR, CRP), laboratory documentation of cervical infection with N. gonorrhea or C. trachomatis.

If necessary, the diagnosis can be confirmed by: a) endometrial biopsy showing endometritis; b) transvaginal sonography demonstrating fluid-filled fallopian tubes, free pelvic fluid, or a tubo-ovarian complex (abscess); or c) laparoscopy. Differential diagnosis may include acute appendicitis, ectopic pregnancy, ruptured corpus luteum cyst with hemorrhage, diverticulitis, septic abortion, adnexal torsion, leiomyoma degeneration, endometriosis, or ulcerative colitis.

Criteria for hospitalization (2) include: surgical emergencies (e.g., appendicitis) that cannot be ruled out, pregnancy, failure to respond to outpatient treatment, suspected noncompliance or intolerance to outpatient treatment, nulligravid status, severe illness (including nausea, vomiting, or high fever), suspected tubo-ovarian or other pelvic abscess. Aggressive antibiotic usage for at least 24 hours is warranted as PID accounts for 15% of female infertility and increases the risk of ectopic pregnancy and chronic pelvic pain (3). A common regimen includes cefotetan (2 g IV every 12 hours) or cefoxitin (2 g IV every 6 hours); plus doxycycline (100 mg PO or IV every 12 hours) (2). A combination of clindamycin, gentamicin, and doxycycline is an alternative regimen (2). Mild PID is often treated as an outpatient with single dose IM/IV ceftriaxone and PO doxycycline or azithromycin.

Gonorrhea

Neisseria gonorrhoeae, a gram-negative intracellular diplococcus, is a commonly found co-infection with chlamydia. Gonorrhea infects the urethra, Bartholin glands, Skene's glands, cervix, epididymis, prostate, anus, pharynx, and conjunctiva. Hematogenous dissemination to joints, skin, meninges, and endocardium may occur (4).

Gonorrhea is one of the most commonly reported bacterial STIs in adolescents (chlamydia is more common, but chlamydia is not a true bacteria). Estimates of 600,000 new infections occur in the U.S. each year in all age groups (2). Overall, the rates of diagnosis are declining, but still remain high among adolescents aged 15 to19 of all racial and ethnic groups (2). In addition to its role in pelvic inflammatory disease, gonorrhea infection also facilitates HIV transmission (2).

Males infected with gonorrhea often present with symptomatic urethritis within 2 to 5 days of exposure, with urethral discharge or dysuria (7). Other manifestations in the male include epididymitis, lymphangitis, or prostatitis. In young women, the endocervical canal and urethra are the primary sites of infection. However, like chlamydia, they are often asymptomatic. If left untreated, it can lead to PID or disseminated infection. Only 10-20% of infected females are likely to present with increased vaginal discharge, dyspareunia, abnormal vaginal bleeding, or signs and symptoms of ascending infection (4). Physical exam may reveal mucopurulent discharge, erythema of the ectropion, and a friable cervix. Ten to 20% of females with acute gonococcal infection will develop PID (7). Individuals with gonococcal salpingitis, as compared to non-gonococcal salpingitis, are more likely to appear more ill, have a fever, and present within 3 days of symptom onset (7). Peritonitis and perihepatitis (right upper quadrant pain and elevated liver enzymes) characterize the Fitz-Hugh-Curtis syndrome, commonly associated with gonorrhea-caused PID.

Disseminated gonococcal infection (DGI) occurs in 0.5 % to 3% of untreated patients (4). DGI is often manifested by polyarticular septic arthritis (joint pain, swelling, tenderness) and skin lesions. Most commonly, the wrist, ankle, knee, and metacarpophalangeal (MCP) joints are involved in an asymmetric and/or migrating fashion. Skin lesions present as a tender, necrotic pustule on an erythematous base over the distal extremities (7).

Gonorrhea can be confirmed by culture, immunochemical, or DNA testing. Gram stain of cervical or urethral discharge generally reveals gram-negative diplococci within or closely associated with PMN leukocytes. Gram stain has a high sensitivity and specificity for males, but the test has a poor sensitivity for females at 30% to 60% because of vaginal bacterial contamination (2,4). Culture is the gold-standard, using antibiotic-containing selective media (e.g., Thayer-Martin medium), which has sensitivities from 80 to 90% (7); however, gonorrhea is fastidious, requiring a special transport and incubation conditions. The non-amplified DNA probe is reported to have sensitivities and specificity up to 97% and 99%, respectively (7). The LCR amplification assay is found to have sensitivities of 95% (7). A test of cure should be performed at approximately 6 weeks after completion of treatment (7).

As gonorrhea has become increasingly resistant to penicillin, quinolone-resistant N. gonorrhoeae (QRNG) is becoming more common in parts of Asia and the Pacific, including Hawaii (2). The CDC's 2002 STD Treatment Guidelines recommend that quinolones no longer be used to treat gonorrhea for infections acquired in Hawaii and California (2). The CDC recommends second- and third-generation cephalosporins such as cefixime (400 mg PO, single dose) or ceftriaxone (125 mg IM, single dose). Partners of patients suspected of having gonorrhea should also be treated to prevent re-infection.

Because patients with gonorrhea are often concomitantly infected with chlamydia, many physicians treat women with mucopurulent cervicitis with an additional regimen of doxycycline or azithromycin to prevent sequelae such as PID. The best prevention of PID is prevention of lower genital tract infection by C. trachomatis and N. gonorrhea (4).

Genital Herpes

Herpes simplex virus (HSV) is a member of the herpesvirus family which includes the Epstein-Barr virus, varicella-zoster virus, and cytomegalovirus. HSV-2 is responsible for most of the genital infections. HSV-1 primarily causes oral infections, but it has been isolated in 10-25% of genital lesions with first-episode genital herpes. HSV infections are transmitted by viral shedding through a peripheral site, mucosal surface, or in genital or oral secretions. Between recurring episodes, HSV virus ascends peripheral sensory nerves and enters nerve root ganglia (7), persisting in a dormant state. The frequency of recurrence of genital lesions after a symptomatic first-episode of genital herpes is high for HSV-2 and less for HSV-1 (2).

At least 50 million people in the U.S. have genital HSV infection (2). In a major study published in the New England Journal of Medicine, 22% of Americans over 12 years old have positive test results for antibodies against HSV-2, the major cause of genital herpes (3,11). This represents a 30% overall increase in the prevalence of HSV-2 since the late 1970s. Furthermore, individuals with HSV-2 are more susceptible to contracting HIV from a HIV-positive partner (3). Most individuals with genital herpes have not been diagnosed (2). Therefore, the disease is often transmitted from asymptomatic individuals, even those who have never had any symptoms (3).

Genital herpes is a life-long, recurring infection. Yet, symptoms vary greatly, both on an individual basis as well as between episodes for the same individual. The primary episode of herpes infection may present with vulvar pain, dysuria, and occasionally urinary retention (4). Systemic symptoms are common such as flu-like symptoms, with malaise, headache, fever, and body aches. Severe complications such as herpes meningitis/encephalitis are rare (4), except in neonates when the risk is much higher.

The most frequent presenting sign of infection is an exquisitely painful pustular, vesicular or ulcerative lesion that spreads rapidly over the external genitalia. In females, lesions may be hidden intravaginally, and patients may not even be aware of its existence. HSV cervicitis occurs in 70-90% of women with their first episode of HSV infection (7). Examination may reveal cervical erythema and friability. Ulcerative lesions may last up to two weeks until crusting or re-epithelialization occurs.

Adolescents should be counseled that genital herpes transmission can occur even when they are asymptomatic. Asymptomatic individuals may shed the virus at the same rate as symptomatic individuals. Recurring infections are generally localized to the genitalia with fewer systemic symptoms.

Diagnosis of herpes infection is best confirmed by viral culture of the lesions (1). However, the sensitivity of the culture declines within a few days of onset as lesions begin to crust and heal. HSV antigen detection tests do not distinguish between HSV-1 and HSV-2 (2). Cytologic detection via the Tzanck smear of the ulcer discharge may demonstrate multinucleated giant cells, though the test itself is not highly sensitive and also does not distinguish between viral types.

During the first several weeks of a primary infection, both type-specific and nonspecific antibodies develop. Type-specific antibodies to HSV-2 are virtually indicative of sexual transmission. Serologic tests may show that the current infection is primary, suggested by a rise in IgM antibodies followed by a rise in IgG antibodies. Because false-negative HSV cultures are common, HSV-2 type-specific serologic tests are useful in determining a diagnosis of genital herpes (2). However, serologic screening for genital herpes in the general population is not indicated (2).

Systemic antiviral drugs partially control the symptoms of herpes episodes for both primary and recurrent disease. Antivirals such as acyclovir, valacyclovir, and famciclovir have demonstrated decreased shedding when taken regularly. However, these medications do not permit a lasting effect. Once the treatment stops, the disease resumes typical pre-treatment frequency and severity of recurrences (2).

Patients with first-episode herpes may eventually develop severe or prolonged symptoms, so treatment is indicated. Recommended regimens include acyclovir, famciclovir, or valacyclovir for 7 to 10 days (2). Treatment for recurrent disease may be administered

episodically or continuously as suppressive therapy. Episodic therapy requires initiation within 1 day of lesion onset. Suppressive therapy reduces the frequency of genital herpes recurrences by 70 to 80% for patients normally with 6 or more recurrences a year (2). Thus, quality of life is often improved in these patients. Suppressive therapy reduces subclinical viral shedding, but does not eliminate the risk.

Counseling is also critical to the management of herpes, to help patients cope and to prevent sexual and perinatal transmission. Patients should be informed that transmission of HSV can occur during asymptomatic periods. Condoms may help reduce the risk, especially when infected areas are covered (2).

Syphilis

Syphilis is caused by Treponema pallidum (subspecies pallidum), a spirochete that cannot be seen by light microscopy. It is identified by darkfield microscopy examination by its characteristic corkscrew motility (4). T. pallidum is transmitted via breaks in the skin or mucus membranes, perinatal transmission, or rarely blood transfusion.

Though syphilitic disease has been significantly curtailed by its sensitivity to penicillin, the incidence has been rising since the 1980s (4). In addition, the rate in adolescent females has increased since the 1990s (4). This is of particular concern considering the high teen pregnancy rates in today's population. Syphilis may be passed to the fetus, resulting in congenital syphilis, which affects brain development and growth. Furthermore, genital ulcer disease increases the risk of HIV transmission (4).

Syphilitic disease is divided into three symptomatic stages: primary, secondary and tertiary syphilis. Primary syphilis presents as a chancre, approximately 1 to 3 weeks after inoculation. A chancre is a highly infectious, painless, ulcerative lesion with well-defined raised borders and an indurated base. It contains large numbers of spirochetes that cannot be visualized by gram stain, but can be seen by darkfield microscopy (4).

Secondary syphilis develops between 4 and 10 weeks after the primary chancre appears. Infected individuals may have systemic complaints such as low-grade fever, malaise, myalgia, arthralgia, and generalized adenopathy. A nonpruritic maculopapular rash may develop on the trunk or extremities, especially the palms and soles. Other anogenital lesions include condyloma lata, which are highly infectious, flat, beefy-like lesions with a broad base (4).

Latent syphilis describes the period after which these systemic symptoms resolve. This period is further divided into early and late phases. Early latent syphilis is defined as less than a year, whereas late latent is longer than 1 year (4). Infectivity is thought to be significantly decreased during the late latent phase, and prolonged antibiotic therapy may be required to adequately manage the slower replicating treponemes (2).

Tertiary syphilis is rarely encountered in adolescents, but serious complications may occur in approximately one-third of patients who enter late latency even though they may no longer be contagious (4). Tertiary syphilis may present with cardiovascular, gummatous and/or neurologic manifestations. Common cardiovascular manifestations of tertiary syphilis include thoracic aortic aneurysm, aortic insufficiency, and coronary ostial occlusion. Chronic inflammatory lesions of tertiary syphilis, called gummas, affect the skin, subcutaneous tissue, and bones. Neurosyphilis, which can occur during any stage, usually includes tabes dorsalis, affecting the spinal tracts controlling proprioception and vibratory sense, and is associated with the Argyll-Robertson pupil (accommodation reflex is intact, but there is no response to direct light).

Diagnosis of early syphilis is done clinically, serologically, or most accurately, by direct visualization on darkfield microscopy. T. pallidum is best visualized by darkfield microscopy of the lesion exudate. Alternatively, direct fluorescent antibody tests can also be used to visualize the treponemes in ulcer smears (2).

During primary and secondary stages, nonspecific serologic tests for non-treponemal (cardiolipin) antibody such as the RPR (rapid plasma reagin) or VDRL (Venereal Disease Research Laboratory) are used as screening tests (RPR has now largely replaced the VDRL test for serum, but not for CSF). Positive results are confirmed with more specific antibody tests including the fluorescent treponemal antibody absorption (FTA-Abs) test, the microhemagglutination-T. pallidum test (MHA-TP), or the hemagglutination treponemal test for syphilis (HATTS). False positive results may occur in patients with various medical problems (e.g., false positive VDRL/RPR occurs with systemic lupus). The differential diagnosis of a positive specific treponemal antibody test includes other treponemal diseases such as pinta, yaws, and endemic syphilis. Yaws is an infection with Treponema pallidum pertenue (T. pallidum, subspecies pertenue), while syphilis is an infection with Treponema pallidum pallidum (T. pallidum, subspecies pallidum). Thus, even the MHA-TP (a specific test for T. pallidum) can be positive in yaws, making the definitive diagnosis of syphilis in yaws endemic areas (e.g., Micronesia), very difficult. According to the CDC, all patients diagnosed with syphilis should be tested for HIV (2).

Diagnosis of neurosyphilis may be difficult as the VDRL test for CSF is high in specificity but low in sensitivity (more false-negatives). In other words, a reactive test would indicate syphilis, but the test may not be reactive in a mildly affected person. Some specialists recommend performing an FTA-Abs test for CSF which is higher in sensitivity (2).

Penicillin is the treatment of choice for syphilis, even for pregnant women (2). Standard treatment for primary, secondary, and early latent syphilis includes parenteral (longer acting) benzathine penicillin G. Late latent and tertiary syphilis requires a longer course of therapy. A test for cure (with the same serologic test) should be performed 3, 6, and 12 months after treatment with a four-fold decline in titer considered to be clinically significant (e.g., from 1:16 to 1:4) (4). Furthermore, patients should be cautioned about the Jarisch-Herxheimer reaction after treatment for early syphilis, due to the sudden rupture of cells containing T. pallidum. Patients may experience self-limiting symptoms such as fever, myalgias, chills, headache, and postural hypotension for the first 24 hours. Management consists of hydration and NSAIDs (4). Identification of sexual partners at risk for contracting syphilis should be directed for serologic testing and/or treatment.

Questions

1. What is the triad of symptoms that suggests pelvic inflammatory disease?

2. What is likely to be the most common STI in adolescents in the United States?

3. Why are adolescents more susceptible to acquiring STIs than adults?

4. What treatment regimen would not be appropriate for an adolescent in Hawaii with confirmed gonococcal cervicitis?
    a. doxycycline 100mg PO BID x 7 days
    b. ceftriaxone 125mg IM x 1 day
    c. cefixime 400mg PO x 1 day; plus azithromycin 1g PO x 1 day
    d. ciprofloxacin 500mg PO x 1 day

5. True/False: Suppressive therapy for genital herpes with acyclovir effectively eliminates viral shedding.

6. Which test is more specific for syphilis? RPR, VDRL, or FTA-Abs (fluorescent treponemal antibody absorption)?

7. What are the criteria for hospitalization of a patient with suspected pelvic inflammatory disease?

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Answers to questions

1. Abdominal pain, adnexal tenderness on bimanual exam, and cervical motion tenderness.

2. Human papillomavirus (HPV) is estimated to be the most common STI among young, sexually active people in the United States, though many HPV infections are asymptomatic. According to the CDC, an estimated 5.5 million people of all ages contract HPV each year in the United States. On the other hand, chlamydia is the most commonly reported infectious disease in the United States.

3. Adolescents adopt high risk behaviors including early onset of sexual activity, multiple sexual partners, or drug/alcohol use which may impair judgment. Adolescents generally are less able to access health care due to embarrassment about their condition, financial constraints, or transportation barriers.

4. d. Quinolones are no longer recommended for the treatment of gonorrhea in Hawaii or infections acquired in Asia. In 2000, the CDC collected 5,461 isolates for its Gonococcal Isolate Surveillance Project (GISP). 14.3% of the GISP isolates in Hawaii were found to be quinolone-resistant N. Gonorrhoeae (QRNG), compared to 0.2% of samples collected within the continental United States and Alaska. Furthermore, since QRNG is becoming more common in West Coast areas, the use of fluoroquinolones in California is probably inadvisable.

5. False. Acyclovir and other antivirals only reduce viral shedding, but they do not eliminate the risk of transmission. Suppressive therapy reduces the frequency of symptomatic genital herpes recurrences by 70% to 80% for patients with 6 or more recurrences a year.

6. FTA-Abs is more specific, but it is still not totally diagnostic of syphilis since patients with yaws will still have a positive FTA-Abs. Other false positive results of FTA-Abs may occur with patients with various medical problems. The differential diagnosis of a positive treponemal antibody test includes other treponemal diseases such as pinta, yaws, and endemic syphilis.

7. Criteria for hospitalization include: surgical emergencies (e.g., appendicitis) that cannot be excluded, pregnancy, failure to respond to outpatient treatment, suspected noncompliance or intolerance to outpatient treatment, nulligravid status, severe illness (including nausea, vomiting, or high fever), suspected tubo-ovarian or other pelvic abscess.

Chapter VI.22. Common Viral Exanthems
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This is a 5 year old male who is referred to your clinic by the school nurse for suspicion of child abuse. The report states that the child's face appears to have been "slapped" repeatedly. From the chart, you note that the patient has no history of trauma or suspicious incidents. He has been seen regularly for well child exams and is up to date on immunizations. The distraught parent states that there have been no recent changes among the family and that the patient has been doing well, other than a moderate tactile fever for two days, alleviated by acetaminophen.

Exam: VS T 38.2, P 95, R 26, BP 110/68, oxygen saturation 99%. Weight and height are at the 50th percentile with normal progress on his growth curve. He is alert, and cooperative in no distress. HEENT exam is significant for slight erythema of his oropharynx. His neck is supple without lymphadenopathy. Heart and lung exams are normal. Examination of his skin is only significant for some slight edema and pinkish red color of his cheeks ("slapped cheek" appearance). There are no bruises or other rashes detected. Exam of his extremities are negative for any signs of injury. Neurologic examination does not reveal any abnormalities.

Following your examination, further questioning reveals an ill cousin with a "rash." Over the next several days, the malar erythema begins to fade and a faint pink rash appear on his trunk and extensor surfaces of his upper extremities. The truncal rash becomes confluent, creating a lacy appearance. Both the fever and rash disappear without any further problems.

An exanthem, originating from the Latin anthos, meaning flower, is a skin eruption occurring as a symptom of an acute infection (1). More than 50 agents (viral, bacterial, or rickettsial) that cause exanthems in children have been identified (2). Therefore, it is not surprising that the febrile child presenting with a "rash" is a diagnostic challenge to many physicians. The goal of this chapter is to provide a systematic framework to approach patients similar to the case outlined above. An accurate diagnosis is possible when close attention is paid to the pattern of patient age, immunization status, prodromal symptoms, character of fever (high-grade, prolonged, chronological relationship to rash, etc), associated manifestations, and the characteristic exanthem. The natural history of each disease is also unique, therefore an attempt has been made to organize the clinical manifestations in chronological order. Several diagnostic lab studies are available, such as specific serologies and rising titers.

Due to the wide differential diagnosis, the scope of this chapter will be limited to common viral exanthems, namely measles, rubella, hand-foot-mouth disease, erythema infectiosum, roseola infantum, and varicella.

Measles (rubeola) is caused by a paramyxovirus which is spread by respiratory droplets produced by sneezing or coughing. Infected persons are contagious for several days before the onset of rash and up to 5 days after the lesions appear. It is highly contagious, resulting in 90-100% transmission among those who are susceptible (2). Prior to the use of the measles vaccine (one component of the MMR), the peak age of incidence was 5-10 years. In underdeveloped countries, up to 45% of cases occur before the age of 9 months. Since widespread immunization began in 1963, measles occurrence is rare. Current small outbreaks in the U.S. occur in unimmunized preschool children and school-aged persons immunized at an early age (who often have not received a second MMR). In Hawaii, most index cases occur in Asian tourists who are not immunized. In the 1980's, there were several outbreaks. The revised recommendation (requirement) for two doses of MMR vaccine prior to school entry has resulted in less than 70 cases of measles in 1998 and 1999 in the U.S. (2). Worldwide, measles is endemic (3).

The measles incubation period is 8-15 days. Measles is rare among immunized patients, especially those who have had two MMR doses. Susceptible individuals exist since some parents have chosen to refuse MMR vaccine for their children. Classically, measles is preceded by the three C's: a hacking cough, coryza (nasal rhinorrhea and congestion), and conjunctivitis, plus photophobia, malaise, and a high fever persisting for several days. The enanthem (mucus membrane eruption) of measles is pathognomonic. Part of the enanthem is called Koplik's spots which appear on or after the second day of fever. The lips, tongue and oral mucosa are hyperemic (red). The Koplik's spots can be described as white spots over the red buccal mucosa (so called, grains of sand in a sea of red) (3). Although pathognomonic, their absence does not exclude measles since this finding is transient, disappearing within 48 hours after onset of the rash (2). The exanthem classically appears on the fourth day of fever. The rash is called "morbilliform" (which means measles-like). This can best be described as non-elevated red spots of varying sizes with a few areas of coalescence. They spread centrifugally and inferiorly to involve the face, trunk, and extremities. Lesions may become confluent, especially on the face, then gradually fade in order of appearance with subsequent residual yellow-tan stain. As the exanthem progresses, systemic symptoms subside (3). There is generalized lymphadenopathy. Otherwise, the exam is unremarkable.

Differential diagnosis includes drug reactions (e.g., Stevens Johnson syndrome), Kawasaki disease, other viral exanthems, secondary syphilis, or scarlet fever (3).

Prevention through prophylactic immunization is the primary approach to measles in the United States. Treatment is otherwise symptomatic (3). In areas of vitamin A deficiency, the World Health Organization (WHO) recommends 200,000 IU of oral vitamin A in three doses over the course of the illness. Immunoglobulin (gamma globulin) is recommended for household contacts, particularly infants less than one year, pregnant patients, and the immunocompromised (2).

Measles is a self-limited infection in most patients. The mortality rate is 0.3% in the United States but ranges from 1-10% in developing countries. Complications are more common in malnourished children, and in those who are immunocompromised. Acute complications include pneumonia (due to measles or a secondary bacterial infection, such as Staph aureus), and measles encephalitis (1 in 800-1000). Subacute sclerosing panencephalitis is a chronic complication (3).

Measles also presents is two other fashions: modified and atypical measles. Modified measles occurs in partially immune individuals. It is characterized by a shorter prodrome and a less severe rash. Atypical measles presents with abrupt onset of high fever, myalgias, and cough. A papular or papulovesicular rash in the extremities begins 2 to 5 days later and spreads centrally. The rash is frequently hemorrhagic and a lobar pneumonia may be present (2).

Rubella, also known as German measles or 3-day measles, is caused by the rubella virus. Transmission is via inhalation of aerosolized respiratory droplets and the period of infectivity is from the end of the incubation period to the disappearance of the rash (3).

Before widespread immunization, this disease was found in children younger than 15 years. Currently it occurs primarily in young adults in hospitals, prisons, colleges, and prenatal clinics. The incidence has decreased by 99% since immunization began in 1969. Rubella is endemic worldwide causing epidemics every 6 to 9 years during the spring.

The incubation period lasts from 14-21 days (2). In 60-90% of adolescents and young adults the exanthem is preceded by anorexia, malaise, conjunctivitis, headache, low-grade fever, mild upper respiratory symptoms, or Forchheimer's sign (petechiae on the soft palate) (3).

The exanthem is characterized by pink macules or papules which appear initially on the forehead, spreading inferiorly to the face, trunk, and extremities in the first day. By the second day, the facial exanthem fades. Truncal lesions may become confluent, creating a scarlatiniform eruption. By the third day the exanthem fades completely (3). On physical examination, lymph nodes are enlarged, particularly postauricular, suboccipital, and posterior cervical, and possibly tender during prodrome. Splenomegaly may also be present (2,3). The differential includes measles, rubella, scarlet fever, erythema subitum, enteroviral infection, and drug reactions.

Rubella is preventable by immunization. If antirubella antibody titers are negative in young women, rubella immunization should be given. In adolescents, pregnancy should be ruled out due to the possible adverse effects of the vaccine on the fetus. Otherwise treatment is symptomatic (2).

In most cases rubella is a mild, self-limiting infection. However, when rubella occurs in the first trimester of pregnancy, infection can be passed transplacentally to the fetus. Of all mothers infected during pregnancy, approximately 50% of fetuses will have manifestations of congenital rubella syndrome, including congenital heart defects, cataracts, microphthalmia, deafness, microcephaly, and hydrocephalus (2,3).

Hand-foot-mouth disease (HFMD) is caused by coxsackie virus. The primary strain is A16 but sporadic cases have been reported with coxsackie viruses A4-7, A9, A10, B2, B5 and enterovirus 71. Highly contagious, it is transmitted from person to person by oral-oral or fecal-oral routes (3). Incubation is 3 to 6 days

The age of onset is usually in children younger than 10 years old, but may occur in young and middle-aged adults. Epidemic outbreaks occur every 3 years. In temperate climates, outbreaks occur during the summer. The prodrome is 12-24 hours of low-grade fever, malaise, and abdominal or respiratory symptoms. Oral mucosal lesions are macules or grayish vesicles (small, less than 0.5 cm circumscribed elevation containing fluid) that evolve to punched-out, painful ulcers that may result in refusal to eat in children. The cutaneous lesions appear on the palms or soles together or shortly after the oral lesions. The sides of the fingers, toes, and buttocks may also be involved. Pink to red macules or papules appear, 2-8 mm in diameter, in a characteristic linear arrangement. They quickly evolve to form vesicles with a clear, watery appearance or yellowish hue. Lesions on the palms and soles usually do not rupture, but other sites may with formation of erosions and crusts (3). The sudden onset of oral and distal extremity lesions is pathognomonic for HFMD. In the absence of an exanthem, the differential diagnosis includes herpes simplex virus, aphthous stomatitis, and herpangina.

Management is symptomatic treatment, including optional topical applications of various local anesthetics to reduce oral discomfort. A diet of vanilla ice cream is the easiest to tolerate. Most commonly, HFMD is a self-limited disease with resultant acquired immunity. A few cases have been prolonged or recurrent. Serious complications are rare, but coxsackie virus has been implicated in myocarditis, meningoencephalitis, aseptic meningitis, paralytic disease, and a systemic illness resembling rubeola. Infection acquired in the first trimester or pregnancy may result in spontaneous abortion. Cutaneous lesions heal without scarring (3).

Erythema infectiosum (EI), also known as Fifth disease, is caused by parvovirus B19. Transmission is via respiratory droplets, with attack rates among close contacts up to 50%. Incubation is 4-14 days. This disease typically affects children 3 to 12 years old but may also appear in non-immune adults. In 20-60% of children, a prodrome of fever, malaise, headache, and coryza appears two days before the rash. Headache, sore throat, fever, myalgias, nausea, diarrhea, conjunctivitis, and cough may coincide with the rash. Pruritus is variably present. Arthralgias may occur but are uncommon. Presentation may differ considerably in adults.

The exanthem has a characteristic "slapped cheeks" appearance. An erythematous, edematous, confluent plaque on the malar face appears first which fades over 1 to 4 days. Erythematous macules and papules then appear on the extensor surfaces of extremities, trunk, and neck. These become confluent causing a lacy or reticulated appearance. Less commonly, lesions may be morbilliform (measles-like), circinate, annular, or rarely form pustules, vesicles, or palmoplantar desquamation. The eruption lasts 5 to 9 days but can characteristically recur for weeks to months, triggered by sunlight, exercise, temperature change, bathing, or emotional stress. Uncommonly, an enanthem with glossal and pharyngeal erythema and red macules on buccal and palatal mucosa may be present. The differential diagnosis includes measles, rubella, scarlet fever, roseola, enteroviral infection, Hemophilus influenza cellulitis, or drug reactions.

Management of EI is symptomatic and is usually a self-limited disease. In patients with hemoglobinopathies or RBC defects, human parvovirus may cause a transient RBC aplastic crisis, manifested by fatigue, pallor, and worsening anemia. Fetal infection may be complicated by fetal hydrops secondary to infection of erythroid precursors, hemolysis, severe anemia, tissue anoxia, and high-output failure. This is a serious concern in schools since children may commonly expose young women who are potentially pregnant (e.g., teachers) to this.

Roseola infantum (exanthem subitum, sixth disease) is caused by human herpes virus 6. This disease usually affects patients under the age of 3 years (2). The incubation period is 5-15 days. The prodrome consists of constant or intermittent high fever with malaise and irritability lasting 3 to 5 days. Occasionally, periorbital edema and febrile seizures are also associated. The exanthem appears after an abrupt defervescence (2). Erythematous to pink macules and papules appear, often arranged in rosettes, mainly involving the trunk with extension to the neck and proximal extremities lasting for 1 to 2 days (2). Treatment is symptomatic (4). Most infants are affected subclinically with two studies showing only 9-17% developing clinical roseola infantum (4). The course is generally benign, but febrile seizures, meningitis, and encephalitis are well-recognized complications. Several case reports have described fulminant hepatitis in primary HHV-6 infection (4).

Varicella (chicken pox) is caused by the varicella-zoster virus (VZV). The period of infectivity extends from the beginning of the prodromal illness through the time that the uncrusted lesions are present (2). Transmission is via respiratory secretions and the fluid produced by skin lesions, either airborne or through direct contact. In the United States pre-vaccine era, 90-95% of individuals acquired VZV infection in childhood with epidemics occurring in the winter and spring. Transmission to susceptible individuals occurred at a rate of 80-90% for household members. Casual contact (e.g. the classroom setting) is associated with attack rates of less than 30% (5).

The incubation period is 14 to 16 days and initial symptoms typically consist of fever, malaise, headache, anorexia, or abdominal pain (2). Temperature elevation is usually moderate but may be as high as 41 degrees C (106 degrees F) (5). The skin lesions appear 24 to 48 hours after the prodromal illness has begun. They begin as intensely pruritic, erythematous macules which rapidly evolve into vesicles containing serous fluid. The exanthem first appears on the face, scalp, or trunk and spreads peripherally. Over a 24 to 48 hour period, the

vesicles umbilicate, the fluid clouds, then transforms into crusts before finally resolving. Healed lesions may leave residual hypopigmentation lasting weeks, but scarring is uncommon. The number can vary from as few as 10 to as numerous as 1500 (5). Ulcerative lesions of the oropharynx and vagina commonly develop concurrently with the exanthem.

Prevention is currently available with the varicella vaccine. The vaccine has reduced the historical transmission rate from 87% to 7% (6). Acyclovir and varicella-zoster immune globulin have been effective in the prophylaxis and treatment of progressive disease, as described below. The course is generally benign, although in certain populations it may be associated with several complications. Perinatal transmission can cause life-threatening infection in the fetus. Progressive varicella is characterized by visceral organ involvement, coagulopathy, severe hemorrhage, and continued lesion development. Severe abdominal pain and the appearance of hemorrhagic vesicles in otherwise healthy adolescents, immunocompromised children, pregnant women, and the newborn may be a red flag for this serious complication (5).

Delivery within one week before or after the onset of maternal varicella frequently results in the newborn developing varicella, which may be severe and requires the administration of varicella-zoster immune globulin and acyclovir. Those who receive prompt treatment have an excellent prognosis. Mothers who had varicella between 8-20 weeks of pregnancy may demonstrate congenital varicella syndrome, characterized by interruption of organogenesis, in particular, the CNS, limbs, and eyes. A characteristic zig-zag scarring, often in a dermatomal distribution, can sometimes be seen (5).

Herpes zoster (also called shingles), due to reactivation of latent VZV, is uncommon in childhood, but more common in teens and adults. When it occurs, it originates in a single dermatomal pattern (e.g., T10), preceded by pain within the dermatome, followed by a dense collection of vesicles within the dermatome. Immunosuppressed children (those receiving immunosuppressive therapy for diseases like malignancy or with HIV) are at higher risk for developing herpes zoster in childhood. The lifetime risk for those with a history of varicella is 10%, with 75% of cases occurring after 45 years of age (5).

Other viruses which commonly cause exanthems include adenovirus (rash, conjunctivitis), echovirus ("Boston exanthem" similar to roseola), and Epstein-Barr virus (see chapter on Epstein-Bar virus). A common rash associated with amoxicillin use is probably related to a viral etiology. Commonly called an "amoxicillin rash", this is a non-allergic rash which occurs when amoxicillin is used in conjunction with some viruses (which are poorly defined). Later, when the viral infection is resolved, amoxicillin use does not result in a rash. This is similar to infectious mononucleosis which results in an impressive rash with amoxicillin/ampicillin use, but no recurrence of a rash with the same antibiotic use, once the viral infection has resolved. Patients are commonly labeled as amoxicillin allergic because of this phenomenon. Most amoxicillin rashes are non-urticarial which is the best (though not perfect) clue that this is probably not due to an allergic mechanism.

Questions

1. Name the type of exanthem depicted in the case described at the beginning of this chapter.
    a. Exanthem infectiosum
    b. Exanthem subitum
    c. Hand-foot-mouth disease
    d. Varicella
    e. Measles

2. Symptoms of congenital rubella include all of the following EXCEPT
    a. congenital heart defects
    b. hydrocephalus
    c. deafness
    d. microphthalmia
    e. zig-zag scarring

3. The mother of a patient comes in to your office stating that she has read terrible things about the vaccinations and doesn't want to give her child any. Which of the following statements is FALSE regarding vaccinations.
    a. The risk of acquiring chicken pox after exposure in the healthy, varicella immunized child is less than 10%.
    b. Vaccines have no adverse affects.
    c. Many vaccines need to be administered more than once.
    d. Rubella incidence has decreased 99% since 1969.
    e. Adverse effects of illnesses prevented by vaccines include death and damage to the central nervous system.

4. A 3 year old patient is seen for several days of fever and refusal to eat. Physical examination reveals a slightly dehydrated child with punched out, painful oral ulcers with associated small red macules on the palms and soles. What type of treatment would you recommend?
    a. Rest and fluids
    b. Rest, fluids, and amoxicillin
    c. Rest, fluids, acetaminophen, and vanilla ice cream
    d. Rest, fluids, acetaminophen, and acyclovir
    e. Rest, fluids, acetaminophen, and ciprofloxacin

5. Your patient has been diagnosed with varicella. Her aunt is pregnant and is not immune to chicken pox. When is the soonest that the aunt can visit the patient?
    a. Immediately, if she is his favorite aunt.
    b. When the lesions crust over.
    c. When the lesions are completely healed.
    d. Two months after the lesions heal.
    e. After the delivery of the fetus.

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Answers to questions
1.a, 2.e, 3.b, 4.c, 5.b

Chapter VI.23. Epstein-Barr Virus Infections
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An 18 year old freshman college student presents to the health center complaining of sore throat and fever for 3 days. She also states that she has been feeling tired for the past week. On physical exam, she is tired and subdued but not toxic in appearance with a temperature of 38 degrees C. Her tonsils are enlarged and erythematous. She has enlarged posterior cervical lymph nodes bilaterally, which are mildly tender to palpation. She has no supraclavicular, axillary, or inguinal lymphadenopathy. Her spleen tip is palpable below the left costal margin. A throat swab is obtained to test for group A streptococcal antigen, which is negative. Laboratory testing reveals a mild leukocytosis with the presence of atypical lymphocytes. A Monospot test is positive. She declines a course of corticosteroid therapy. Her symptoms improve in a week.

The Epstein-Barr virus (EBV) causes a broad spectrum of disease in humans with several clinical syndromes. Perhaps the best known is the one illustrated in the case above, the syndrome of infectious mononucleosis. This is an acute illness that results from primary infection with the virus. It is characterized by the triad of sore throat, fever, and lymphadenopathy. The name is derived from the mononuclear lymphocytosis with atypical appearing lymphocytes that accompany the illness.

The EBV virus is ubiquitous, infecting more than 95% of the world's population. Its clinical manifestations depend on the age when the infection is first acquired. Most infections occur during infancy or early childhood. These are often asymptomatic or indistinguishable from other childhood illnesses. Among affluent communities, however, primary infection may be delayed until adolescence or young adulthood. This is when the classic syndrome of infectious mononucleosis often manifests. Almost all adults over age forty have been infected with EBV and show serologic evidence of prior infection.

The EBV virus is a member of the herpes virus family. EBV is also known as human herpes virus-4 or HHV-4. Like other herpes viruses, it establishes a lifelong latent infection. The virus is transmitted in oral secretions and is acquired from close contact such as kissing or exchange of saliva between children. It initially infects epithelial cells in the oropharynx, where viral replication occurs and lysis of the epithelial cell results in release of new virions into the circulation. The virus then infects B lymphocytes in the peripheral blood and the reticuloendothelial system, including the liver, spleen, and lymph nodes. It is in these cells where the virus establishes latency, via formation of a viral episome. The host mounts a cell-mediated immune response to control the number of proliferating infected B lymphocytes. The atypical lymphocytes seen in infectious mononucleosis are activated CD8 T-cells, which exhibit suppressor and cytotoxic functions in response to the infected B cells. Infection is thus controlled but not abolished. Reactivation may occur intermittently with viral shedding in oral secretions of affected individuals.

The incubation period of infectious mononucleosis is 30-50 days. The onset of symptoms is often insidious, with a prodrome of malaise, headache, fatigue, fever, sore throat, anorexia, and myalgia. Patients seek medical attention with worsening sore throat and fever. On physical exam, the most common finding is lymphadenopathy, which is present in 90% of cases. It often occurs in the cervical region, particularly the posterior cervical chain, but may also be generalized with involvement of submandibular, epitrochlear, axillary, and inguinal lymph nodes. Lymph nodes are not spontaneously painful but may be mildly tender to palpation. Fever and pharyngitis occur in most patients. Pharyngitis may be moderate to severe with tonsillar enlargement and exudate. Abdominal exam may reveal splenomegaly in 60% and hepatomegaly in 10%. Patients treated with ampicillin/amoxicillin for presumed bacterial infection characteristically develop a maculopapular rash, which may be useful in diagnosis, but it is also an annoying adverse effect that often results in an inappropriate diagnosis of penicillin allergy.

The diagnosis of infectious mononucleosis may be made by clinical history, physical exam, and typical laboratory findings. Greater than 90% of patients will have leukocytosis, with white blood cell counts ranging from 10,000 to 20,000. Atypical lymphocytes usually account for 20-40% of the total number. These cells appear larger, with eccentrically placed nuclei and a larger amount of cytoplasm compared to typical lymphocytes. Mild elevation of liver enzymes occurs in 50%.

EBV-associated infectious mononucleosis is associated with the transient production of heterophil antibodies. These are IgM antibodies from the patient's serum that cause agglutination of red cells from sheep or horse serum. The most widely used test is the Monospot (trademark), a qualitative rapid slide test which detects horse red cell agglutination (i.e., the modern equivalent of the heterophil antibody). The sensitivity and specificity of this test is greater than 95% for diagnosing EBV-associated infectious mononucleosis. Children with symptomatic primary EBV infection are often heterophil negative. Ten percent of EBV-associated infectious mononucleosis may be heterophil- negative. Certain organisms may cause an infectious mononucleosis-like syndrome but are not associated with formation of heterophil antibodies, such as cytomegalovirus, T. gondii, adenovirus, viral hepatitis, HIV, and rubella.

The host also produces antibodies specific to the EBV virus. These are unnecessary for the diagnosis of infectious mononucleosis when the Monospot test is positive. These may be useful to clarify the diagnosis of heterophil-negative cases, or for atypical EBV infections when the Monospot test is often negative. Multiple EBV-specific antibody tests are available, including tests for viral capsid antigen (VCA), early antigen (EA), and EBV nuclear antigen (EBNA). The presence of IgM antibodies against viral capsid antigen signifies acute infection, while the presence of IgG antibodies signifies recent or past infection.

Infectious mononucleosis usually resolves in 2-3 weeks, although malaise may persist for weeks to months. Treatment is primarily supportive, with rest during the acute stage of illness and symptomatic care. Contact sports should be avoided while splenomegaly is present due to the risk of splenic rupture, although the incidence of this is low at less than 0.5%. Treatment with acyclovir or corticosteroids has not been proven to be of benefit in uncomplicated cases. Corticosteroids may be considered for severe complications of EBV infection, which are rare. Complications may include marked tonsillar inflammation with impending airway obstruction, massive splenomegaly, myocarditis, autoimmune hemolytic anemia, aplastic anemia, thrombocytopenia, neutropenia, hemophagocytic syndrome, meningitis, and encephalitis. EBV infection has been identified as a possible causative agent for chronic fatigue syndrome, but there is no strong evidence to support this.

EBV has been linked with benign and malignant proliferative disorders, particularly in patients with immunodeficiencies such as HIV, transplant recipients, severe combined immune deficiency, or Wiskott-Aldrich syndrome. The absence of an intact cell-mediated immunity in these patients allows the uncontrolled proliferation of EBV-infected B lymphocytes. Examples of benign disorders include oral hairy leukoplakia, which occurs primarily in adults with HIV and presents with raised, white lesions on the tongue, and lymphoid interstitial pneumonitis, which occurs primarily in children with HIV and is characterized by the presence of diffuse interstitial pulmonary infiltrates. Examples of malignant disorders that have been associated with EBV include nasopharyngeal carcinoma, the most prevalent cancer among adult males in southern China, and African Burkitt lymphoma, the most common childhood cancer in equatorial east Africa. Genetic and environmental factors may play a role in the increased incidence of these diseases in these areas. EBV has also been associated with lymphoma in immunosuppressed patients.

Questions

1. A 16 year old male presents with sore throat, fever, and cervical lymphadenopathy. A throat culture is done which is positive for group A streptococcus. Treatment is initiated with penicillin. He returns two days later with worsened symptoms, despite taking the medicine. Which of the following is the most appropriate step to do next?
   a. Switch to azithromycin.
   b. Obtain a CBC and Monospot.
   c. Check anti-VCA, anti-EA, and anti-EBNA titers against EBV.
   d. Assume the patient has infectious mononucleosis and start acyclovir and prednisone.

2. Which of the following is FALSE regarding EBV infection in young children?
   a. Primary infection is usually asymptomatic.
   b. Heterophil antibodies are usually positive.
   c. Immunocompromised patients are at risk for lymphocytic interstitial pneumonitis
   d. Complications are less common than in adults.

3. Which syndrome has NOT been found to be associated with EBV?
   a. Nasopharyngeal carcinoma
   b. Oral hairy leukoplakia
   c. Aplastic anemia
   d. Kaposi's sarcoma

4. An 18 year old female presents with malaise, fever, sore throat, and lymphadenopathy. Her CBC reveals atypical lymphocytosis, but her Monospot test is negative. Which of the following statements is TRUE?
   a. The Monospot test is not a highly sensitive test.
   b. Her symptoms may be due to primary infection by cytomegalovirus (CMV).
   c. There is no role for EBV-specific antibodies in making the diagnosis.
   d. The atypical lymphocytes represent circulating infected B lymphocytes.

5. Which of the following statements about EBV infection is TRUE?
   a. The syndrome of infectious mononucleosis results from primary infection with the virus.
   b. Infection usually occurs via contact with the blood of an affected person.
   c. About 25% of older adults show serologic evidence of prior infection.
   d. Splenic rupture is a frequent complication in EBV-associated infectious mononucleosis.

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Answers to questions

1. The answer is b. In this case, the group A streptococcus probably represents colonization rather than the etiology of the patient's symptoms. Infectious mononucleosis may have a similar presentation to streptococcal pharyngitis, and must be considered if a patient is not responding clinically to treatment with antibiotics. Diagnosis may be made with a Monospot test as well as the presence of atypical

lymphocytes on CBC. EBV titers are not usually needed in diagnosis, but may be considered if the Monospot is negative and EBV infection is to be ruled out. Treatment with acyclovir or corticosteroids has not been proven to be of clinical benefit in uncomplicated cases of infectious mononucleosis.

2. The answer is b. Primary EBV infection occurs more commonly in childhood and is often asymptomatic. In children who do develop symptomatic EBV infection, heterophil antibodies are more often negative. Lymphocytic interstitial pneumonitis may occur in children with HIV. Complications occur less commonly in children than in adults.

3. The answer is d. The first three have all been found to be associated with EBV infection. Kaposi's sarcoma is associated with a different human herpes virus, referred to as human herpes virus-8 or HHV-8.

4. The answer is b. The Monospot test is a highly sensitive test, although ten percent of EBV-associated infectious mononucleosis may be negative. There are also a number of organisms that may cause an infectious mononucleosis-like syndrome but are not associated with formation of heterophil antibodies. The most common cause of a heterophil-negative infectious mononucleosis-like syndrome is CMV, which this patient likely has. Obtaining antibody titers specific against EBV and CMV may clarify the diagnosis. The atypical lymphocytes that may be seen with either EBV or CMV infection represent activated T lymphocytes, which proliferate in response to infected B lymphocytes.

5. The answer is a. The syndrome of infectious mononucleosis results from primary infection with EBV, particularly when it is delayed until adolescence or young adulthood. It is usually transmitted through close contact with oral secretions of an infected individual. The virus is ubiquitous, and almost all adults over age 40 show serologic evidence of prior infection. Splenic rupture is a rare complication of EBV-associated infectious mononucleosis.

Chapter VI.24. Polio
Rodney K. Yamaki

This is a 4-1/2 month old female who presents to the ER with weakness in her right leg. She is afebrile and does not appear to have any difficulty breathing. Her right leg appears flaccid and no DTR or Babinski can be elicited although sensation is intact. The tone, movement, sensation, and reflexes of her other limbs are normal. Her cardiovascular, respiratory and abdominal examination are normal. Upon further investigation, her father reports that she had a cough and fever of 38.3 C that resolved one week prior to presentation. Her father also notes both a normal birth history and appropriate well baby check ups. Her immunization records are up to date and at her 4 month visit (2 weeks prior to presentation), she received her 2nd doses of HiB, DTaP, OPV and pneumococcal vaccine.

CBC and Serum IgG/IgA/IgM are normal and CSF demonstrates elevated protein with normal glucose. Radiographs of her spine and right lower extremity are unremarkable. Electrophysiological studies (electromyography and nerve conduction studies) show absent motor responses to stimulation of her right tibial nerve. Fecal samples culture the Poliovirus type 3. It is then sent to the CDC where the poliovirus is identified as a vaccine strain of poliovirus (not the "wild-type" strain).

She is admitted to the hospital for monitoring. Her immunocompromised grandfather who changes diapers occasionally is informed about her spinal polio and encouraged to seek medical attention. During her inpatient care, mechanical ventilation is not required and she does not experience any urinary or fecal difficulties. One week after admission, she is discharged with mild residual weakness of her right leg.

Poliomyelitis is a disease that can be traced throughout recorded history. Egyptian murals note a man with an atrophied, shortened leg that appear to describe the late effects of polio. However, its first clinical description occurred in 1789 when Michael Underwood ascribed this condition to the disease that affected the lower extremities of children. Polio epidemics plagued the world over the next centuries. It is difficult for those of us living in the post-vaccine era to imagine the extent of these outbreaks, but an example is the 1952 epidemic that infected more than 50,000 Americans with a mortality rate of about 12% (1). Fortunately, the incidence of polio finally peaked in the 1950s and 1960s with the vaccine discoveries of Jonas Salk and Albert Sabin. The widespread use of these vaccines has dramatically decreased its incidence and has allowed us to target polio for global eradication.

Poliomyelitis is a highly contagious and infectious illness that exclusively affects humans. It is caused by 3 different serotypes of the poliovirus: P1 (majority of cases), P2, and P3. All of the poliovirus subtypes are included in the Picornaviridae family (pico=small, RNAviridae=RNA virus). Similar to other enteroviruses, the poliovirus is a transient inhabitant of the gastrointestinal system and is able to tolerate low pH settings. As the family name suggests, the poliovirus is relatively small. It is non-enveloped and its protein capsid of icosahedral symmetry measures less than 30 nm in diameter. Furthermore, its family name describes its genome as being RNA; specifically, it is single and positively stranded.

After the poliovirus attaches to specific human cell receptors, this single, positive stranded RNA is uncoated in the cytoplasm where it can be directly translated into products such as progeny protein capsids and replication enzymes. The replication of the genome itself is through a complementary negative strand. Once the genome is replicated, it is assembled into the protein capsids where the virions accumulate until they are released upon the death of the host cell.

The communicability of the poliovirus is mainly through the fecal-oral route, but oral-to-oral transmission is possible. Following exposure, the poliovirus infects the tissues of the oropharynx. It is then secreted into saliva and swallowed, allowing the virus to spread to the gastrointestinal system. There, the virus replicates and can subsequently invade the local lymphoid tissue, the bloodstream, and the CNS. The response to the infection is variable as seen in the range of clinical presentations. In a minority of patients, the virus can spread to the nervous system possibly through viremia or through retrograde transport along motor axons. Poliomyelitis has a selectivity toward the motor neurons of the anterior horn and the brain stem. It is the cell destruction at these sites that cause the paralysis that is associated with polio.

There are various responses to polio infections. The first subgroup encompasses the vast majority of polio cases. Up to 95% of polio patients have inapparent or asymptomatic infections (2). While these patients have no symptoms, they are infectious and briefly shed the virus in their stool to their contacts. The second subgroup is the abortive poliomyelitis which occurs in 4-8% of the cases (2). This subset is also spared CNS complications but can present with symptoms of malaise, anorexia, nausea, vomiting, headache, sore throat,

constipation, and diffuse abdominal pain. These patients usually undergo a complete recovery in less than a week. The third subgroup is the nonparalytic aseptic meningitis form of poliomyelitis which includes 1-2% of all cases (2). This group exhibits prodromal symptoms that are similar to those in abortive poliomyelitis but is complicated by posterior muscle stiffness of the neck, back, and limbs which can be accompanied by paresthesias. These signs of meningeal irritation and muscle spasm will typically resolve after 2-10 days. The final subgroup conjures up images of what most people think as the typical polio patient. Less than 2% constitute this form of poliomyelitis (2). Paralytic symptoms can present 1-10 days after initial prodromal symptoms. These paralytic symptoms are usually asymmetrical and include decreased deep tendon reflexes with no changes in cognition or sensation. Paralytic polio can be further separated into three types: spinal polio, bulbar polio, and bulbospinal polio. Spinal polio is the most common form and usually involves an asymmetric involvement of the legs. Cranial nerves can also be involved along with the muscles of respiration. Of historical interest, the "iron lung" was a negative pressure ventilator fitted outside the patient's body to chronically ventilate patients with respiratory paralysis. Of contemporary concern is that patients who contracted paralytic polio as children can develop a post-polio syndrome decades later.

Polio has been eradicated from North America so it is unlikely that we will ever see a case. In regions where polio still exists, poliomyelitis should be considered in an unimmunized or partially immunized patient with the clinical symptoms listed in the prior section. The choice of diagnostic tests include stool and throat cultures with greater success in isolating the virus from the stool. If the paralytic form of the polio is suspected, two or more samples are collected at least 24 hours apart and should be obtained within the first 14 days of symptoms. If the poliovirus is identified through the cultures, the isolate should then be sent to the Centers for Disease Control and Prevention to differentiate the naturally occurring "wild type" from the oral attenuated vaccine strain (which can cause poliomyelitis, rarely). In the absence of an isolate, poliomyelitis can be diagnosed with paired measurements of acute and convalescent sera. It is possible to witness a four fold or more increase in antibody titers. However, these results do not differentiate the "wild type" from the vaccine strain and can at times be equivocal. If CSF is obtained in the workup, it rarely isolates the poliovirus, but it can demonstrate pleocytosis with mildly elevated protein.

Treatment involves isolation of the hospitalized patient, strict bed rest, symptomatic pain relief, respiratory support as needed, and subsequent rehabilitation of affected muscles.

The last case of "wild type" poliomyelitis in the United States occurred in 1979. Through the efforts of the Global Polio Eradication Program, the number of endemic countries has decreased from 125 in 1988 to 10 as of 2001. In addition, the number of reported polio cases has substantially decreased over the same period (3). These efforts now focus on eliminating the virus from the Indian subcontinent and Africa through the use of the polio vaccine.

The dramatic decreases in the incidence of polio are attributed to the two types of vaccines that are currently available in the United States: the inactivated poliovirus vaccine (IPV) and the oral poliovirus vaccine (OPV).

IPV is also known as the Salk vaccine. Because it contains the inactivated forms of all three serotypes, it confers effective immunity to the polioviruses. Furthermore, since it does not contain the live virus, it is safe for use in immunocompromised patients and their contacts. It also does not cause the vaccine associated paralytic poliomyelitis (VAPP) seen with the oral vaccine. The disadvantages of the IPV are the exclusive administration through injection, less gastrointestinal immunity, and an unknown duration of immunity (4). Decreased gastrointestinal immunity could allow possible infection of the "wild type" strain through the GI tract. While the immunized person would be protected from the paralytic form of poliomyelitis, the patient would shed the poliovirus to other contacts. This lack of gastrointestinal immunity is part of the reason that the OPV is used by the World Health Organization for its global eradication efforts.

OPV is also referred to as the Sabin vaccine. OPV also provides effective immunity against all three serotypes of the poliovirus. The advantages of the oral vaccine include easier administration, probable lifelong protection, and better gastrointestinal immunity (4). The main disadvantage of the OPV is the risk of VAPP. Vaccine Associated Paralytic Poliomyelitis occurs when the live oral virus reverts to a virulent form. The risk of this occurrence is estimated to be 1 per 2.4 million doses distributed (125 cases for 303 million doses distributed) with most cases usually occurring after the administration of the first dose (4). This translates to five cases of VAPP reported in 1997 and two cases in 1998 (5). VAPP is also associated with patients who are immunocompromised. Because of this risk, the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP), now recommend an all-IPV schedule for routine childhood polio vaccination in the United States. All children should receive four total doses of IPV with single doses at ages: 2 months, 4 months, between 6-18 months, and between 4-6 years.

There are special circumstances that allow the use of the oral vaccine. These include: 1) Mass vaccination campaigns to control paralytic poliomyelitis outbreaks; 2) Unvaccinated children traveling to endemic or epidemic areas without enough time to administer 2 doses of the IPV; 3) Children whose parents do not accept the immunization schedule can receive the OPV for the third and/or fourth doses only; 4) Depletion of remaining supplies of OPV to children for their third and/or fourth doses although it is preferred that the OPV reserves be used preferentially on 4-6 year old for their fourth dose (6).

There are certain precautions and contraindications to childhood polio immunization. Immunocompromised patients should only receive IPV. Similarly, household contacts (immunocompromised patient in the household) should not receive the OPV because of the risk of excreting live polio vaccine virus and exposing household contacts. If these people happen to be vaccinated with the OPV, they should have minimal close contact with the immunocompromised person for between 4-6 weeks after immunization. Immunization should also be avoided during pregnancy because of the possible adverse effects of the vaccine on the fetus. If vaccination is required during pregnancy, IPV is recommended. Finally, since IPV contains trace amounts of streptomycin, polymyxin B, and neomycin, IPV is contraindicated for those with reactions to these antibiotics or those who have had prior reactions to previous doses. Both vaccinations can be used with breastfeeding and during bouts of mild diarrhea (7).

Those affected with acute paralytic poliomyelitis can experience Post-Polio syndrome (PPS) an average of 35 years after an infection. It was first described in the French medical literature in 1875. In a commentary on one of these cases, neuropathologist Jean Martin Charcot astutely hypothesized that one spinal disorder laid a patient more susceptible to a subsequent spinal disorder due to the overuse of the involved limbs. For reasons unknown, the late sequelae of paralytic poliomyelitis were not investigated further and prior to 1980, there was not even a name associated with this condition. In 1987, the National Health Interview Survey estimated more than 640,000 survivors of paralytic polio in the United States with more than half of these survivors demonstrating new late manifestations of post-polio syndrome (8). It is unclear how many of these polio survivors are still alive today, nor is it clear the added contribution of immigrants, refugees, and illegal aliens moving to the United States who are also survivors of paralytic polio.

Risk factors for PPS include: the severity of the acute poliomyelitis paralysis, age at onset of the acute poliomyelitis (higher risk with adolescent and adult onset), the amount of recovery, and greater physical activity during the intervening years (8). In a summary of four major studies, the frequency of symptoms were consolidated into the following data: fatigue 62-89%; weakness in previously affected muscles 54-87%; weakness in previously unaffected muscles 33-77%; muscle pain 39-86%; joint pain 51-79%; cold intolerance

29-56%; muscle atrophy 28-39%; new difficulties with walking 52-85%; new problems with climbing stairs 54-83%; new difficulties with dressing 16-62% (9).

Although there is no definitive origin of PPS, one leading hypothesis suggests that once the motor neurons are reinnervated, the excessive metabolic stress over the years eventually leads to the eventual dropout of the motor neurons. Many of us associate The March of Dimes with preventing birth defects and infant mortality. However, The March of Dimes was originally created to combat the polio epidemics. The March of Dimes continues its polio efforts as evidenced by its involvement in the 2000 International Conference on Post Polio Syndrome which developed the following diagnostic criteria (10).

1. Prior paralytic poliomyelitis with evidence of motor neuron loss, as confirmed by history of the acute paralytic illness, signs of residual weakness and atrophy of muscles on neurologic examination, and signs of denervation on EMG.
2. A period of partial or complete functional recovery after acute paralytic poliomyelitis, followed by an interval (usually 15 years or more) of stable neurologic function.
3. Gradual or sudden onset of progressive and persistent new muscle weakness or abdominal muscle fatigability (decreased endurance), with or without generalized fatigue, muscle atrophy, or muscle and joint pain.
4. Symptoms persist for at least a year.
5. Exclusion of other neurologic, medical and orthopedic problems as causes of symptoms.

It is very unlikely that we will witness patients with acute poliomyelitis. The wild-type poliovirus has nearly been eradicated from the globe, and due to current vaccination recommendations, VAPP can be avoided by using IPV. Although this discussion of Post-Polio Syndrome is beyond the scope of a pediatrics textbook, modern experiences with poliomyelitis will more likely to be with adults with post-polio syndrome.

Questions

1. The 3 serotypes of the poliovirus belong to which family of viruses?

2. Of the 4 acute clinical presentations (asymptomatic, abortive, nonparalytic aseptic meningitis, or flaccid paralysis poliomyelitis) which is the most common?

3. What are the AAFP, AAP, ACIP childhood immunization schedule recommendations for polio vaccination?
   a. Exclusive OPV
   b. Exclusive IPV
   c. Mixed IPV/OPV (first two doses being with IPV)
   d. Four doses of the Sabin vaccine

4. Which vaccination (OPV or IPV) should be used for the following clinical situations?
   a. Vaccination of children in an endemic country.
   b. Doctor has remaining OPV supplies. Third does for an infant living with an agammaglobulinemic Grandpa.
   c. Doctor has remaining OPV supplies. Third dose for a child whose parents refuse any more injections.
   d. Doctor has remaining OPV supplies. 2 month old's first polio immunization.
   e. Outbreak of "wild type" polio in the United States

5. Describe the proposed pathophysiology of post-polio syndrome.

6. True/False: The March of Dimes is named after the campaign where Americans mailed in their dimes to fight polio.

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Answers to questions

1. Picornaviridae family (Pico=small, RNAviridae=RNA virus).
2. Asymptomatic presentation is up to 95% of the cases.
3. The correct answer is b, exclusive IPV immunization.

4a. OPV (for endemic countries).
4b. IPV (Household contact, especially since Grandpa might be changing the diapers).
4c. OPV (May receive 3rd and/or 4th oral doses).
4d. IPV (Immunization through all IPV schedule).
4e. OPV (Mass vaccination campaign to control outbreaks).

5. The proposed mechanism includes the dropout of neurons that were reinnervated after the initial paralytic poliomyelitis infection due to increased metabolic stresses.

6. True. The March of Dimes was originally named the National Foundation for Infantile Paralysis.

Chapter VI.25. Rabies
Grant L.Y. Chen, MS

An 8 year old male presents to the ER with headache, temperature of 39.5 C, chills, and vomiting. His mother reports that he had experienced worsening headache over the past 2 days. Meningitis is a concern, so an LP is performed which shows 20 RBCs, 0 WBC, a mildly elevated protein and normal glucose. Therapy is started with broad spectrum antibiotics, and he is admitted to the floor. Two days later, his mental status worsens in spite of therapy, so a repeat LP is performed. The repeat reveals: opening pressure of 28 cm water, clear fluid, 6 WBC, (84% lymphs), glucose 92 mg/dl and an elevated protein. There are no focal deficits on neurological examination, but since he is agitated and combative, he is sedated and intubated. Acyclovir is added to his therapy for the possibility of encephalitis.

Two days later, his fever drops, and he became alert at times, but he is still agitated. Further history from the mother reveals that the family had recently moved from the Philippines. The mother denies a history of dog bites, but notes that the child would occasionally play with bats that were caught by his grandparents for him to be used as pets. She denies bat bites, but states that there may have been skin to bat contact when the bat would land on the child. Based on this history, his saliva is sampled, along with a skin biopsy from his neck. Immunofluorescent staining of the skin reveals the presence of rabies antigen, and rhabdovirus is present in his saliva after reverse transcription and PCR testing. The family is notified of the diagnosis and he continues to progressively deteriorate, passing away 10 days after admission. Postmortem autopsy of cerebellar tissue reveals the presence of basophilic inclusion bodies. The brain is soft and edematous. PCR analysis of the tissue at the CDC implicates a strain of the rabies virus associated with the Philippines.

Rabies is a disease whose presence has been noted throughout recorded history. Rabies is inevitably fatal by the time that significant symptoms appear, which is why prophylaxis must be started before symptoms appear. It causes a highly fatal acute encephalitis, causing approximately 35,000 deaths each year worldwide. Rabies virus belongs to the Rhabdoviridae family. Animal cases of rabies have been reported in all states with the exception of Hawaii, which continues to be rabies free. Human acquisition of rabies in the United States is a relatively rare occurrence, as only 32 cases of rabies were recorded between 1980 and 1996, occurring in 20 states (1). However, the yearly mortality rate in the Philippines is approximately 340, and in India, more than 25,000 people fall victim to rabies each year.

The normal mode of transmission of this disease has been by direct contact between animal and man. The animal implicated most frequently has been the dog, but other common zoonotic reservoirs of the disease include raccoons, bats and skunks. It is estimated in the Philippines that 10,000 dogs are infected each year (3). The primary wild reservoir of rabies in the United States is the raccoon. The rabies virus reproduces in both human and animal reservoirs, and is found in not only nervous tissue, but also in saliva, which provides the primary method for transmission of the virus. It is notable that the titer of rabies virus is much higher in skunks than other animals (5). Also, cats, while less frequently infected, have sharper teeth that cause deeper puncture wounds. In the case of transmission from bats, it is believed that transmission may occur through inhalation of aerosolized bat feces (highest risk in caves with high bat populations), and also through direct skin-to-skin contact. Non-animal associated transmission of rabies is extremely rare, and has occurred by means of corneal transplantation from an unknowingly infected donor who died from rabies (diagnosed after the corneal transplant recipients were diagnosed with rabies at post-mortem).

Rabies spreads centripetally from the bite wound (usually an extremity) into the CNS, moving at an estimated rate of 1-2 cm/day (8). The period between the inoculation of the virus into the victim and its invasion of the CNS is the incubation period. The median incubation period is 85 days (range 53-150 days) (1), although molecular biological analysis reveals that the incubatory stage can last up to 7 years (5). It is not known what mechanism modulates the rate of rabies virus travel from the periphery to the central nervous system. It is believed that the primary factor involved in determining whether or not the bitten individual is inoculated with the virus is whether or not the virus makes contact with muscle. Prior to the invasion of the nervous system, the virus reproduces in the muscle tissue, subsequently invading the motor neurons. Bat rabies, unlike canine rabies, possesses the ability to replicate in skin and connective tissue, explaining why non-bite inoculation is prevalent in bat exposures (8).

The first signs and symptoms of rabies are often nonspecific, including fever, sore throat, chills, malaise, anorexia, headache, nausea, vomiting, dyspnea, cough, and weakness. A characteristic symptom is the presence of paresthesia in the area local to the bite. This is thought to be early ganglionic invasion of the virus.

There are two presentations of canine rabies, a "furious" (encephalitic) or "dumb" (paralytic) form. Both forms are invariably fatal, with the furious form causing death within a week, and the dumb form causing death within 2 weeks. Characteristic of furious rabies is high fever, hyperactivity, hypersexuality, including an increase in sexual appetite and priapism of several days, along with autonomic dysfunction, piloerection, and pupillary abnormality (1,5,6,8). The autonomic dysfunction also includes excess salivation, which can produce the "foaming at the mouth" that is often said to accompany rabies. The dumb form progresses from the peripheral weakness to a generalized craniospinal weakness (1,6,8). The late features of dumb rabies are typically encephalitic.

Bat rabies differs from canine rabies not only in method of inoculation, but also in presentation. Patients with bat rabies have a high incidence of focal brainstem signs and myoclonus, and may display hemiparesis, hemisensory deficits, ataxia, chorea, or Horner's syndrome (1,8). In contrast, victims of canine bite rabies display only focal weakness, usually in the limb that was bitten.

In addition to the clinical findings of rabies, a histopathologic finding is the presence of Negri bodies. These are inclusion granules found in cells of the CNS, most often within the pyramidal cells of Ammon's horn, or the Purkinje cells in the cerebellum. They are described in the literature as either eosinophilic or basophilic inclusions, and are cytoplasmic inclusion bodies containing viral nucleoprotein. The presence of Negri bodies is variable, as non-rabid tissues have displayed inclusions that are indistinguishable from Negri bodies, while rabid tissue from animals have shown Negri bodies in only 50% of samples taken.

Thus, the most reliable test for rabies prior to the appearance of symptoms remains the direct fluorescent antibody test (DFA). However, the DFA requires brain tissue, and is therefore performed post-mortem. It is the test of choice for the testing of rabid animals. For humans, it is necessary to perform multiple tests to diagnose rabies before death. The two main tests are testing for the virus in saliva by PCR, or testing the blood serum or spinal fluid for antibodies to rabies virus. Additionally, skin biopsy specimens may display rabies antigen within cutaneous nerves (10). The small number of rabies cases in the United States undoubtedly contributes to the lack of clinical suspicion by the physician, but it is important to remember that any patient presenting with encephalopathy of unknown cause should be considered to potentially have rabies, even in the absence of known exposure to the virus through animal bites. The validity of this statement is further justified by noting that 12 of the 32 deaths (37.5%) in the US attributable to rabies were not diagnosed until after the death of the patients, and of these 12 cases, 6 were not diagnosed until several weeks after death (1). Additionally, while all 32 fatal rabies cases in the US between 1980 and 1996 were seen by their physicians on an outpatient basis prior to the onset of terminal symptoms, not one of them received a complete set of rabies prophylaxis post-exposure. As a further reminder of the importance of clinical suspicion for pediatricians, a 1990 study showed that animal bites were the fourth leading cause of accidents in children 9 years old or less.

As rabies is a uniformly fatal disease once the symptomatic stage of the disease has developed, it is important to provide pre-exposure, and if necessary, post-exposure prophylaxis for patients. The origins of modern rabies treatment lie in Louis Pasteur's work with live attenuated rabies virus in the 19th century. After discovering the transmissibility of rabies by nervous tissue inoculation, Pasteur determined that passage of the virus from dogs to monkeys attenuated the virus, while transmission from rabbit to rabbit increased the virulence of the strains. By utilizing his attenuated strain on 9 year old Joseph Meister, he was able to attain "the happy outcome" now known to all.

Following Pasteur's work, the duck embryo rabies vaccine was produced in 1955, and was used for prophylaxis for more than 25 years, proving effective when combined with equine rabies immunoglobulin (RIG). However, this therapy caused allergic reactions in response to the avian antigens, required 21-23 doses, was very painful, and the equine origin of the RIG could cause serum sickness (5).

Modern rabies immunization consists of two types of products: Active immunization with rabies vaccine (HDCV-human diploid cell vaccine, PCECV-purified chick embryo cell vaccine, or RVA-rabies vaccine adsorbed), and rabies immune globulin (RIG). The modern version of the RIG is derived from the plasma of hyperimmunized human donors, thus eliminating the equine antigens present in the previous version of the RIG. RIG produces a rapid, passive immunity with a half-life of approximately 21 days. On the other hand, rabies vaccine creates an active immune response that takes 7-10 days to produce, and lasts for 2 or more years. The recommended pre-exposure vaccination is three 1.0 ml injections of HDCV IM (deltoid) on days 0,7, and 21 or 28. Should immunosuppressed individuals become exposed to rabies, they should be treated as indicated, and titers should be taken to confirm development of rabies antibodies. Booster doses of the vaccine may be given every 2 years if the antibody titers in the patient are decreased. Should pre-vaccinated persons become exposed to rabies, they should NOT be given RIG, as an amnestic response will develop. Treatment of persons known to be exposed to rabies is threefold: First, there should be an immediate and thorough cleansing of the wound with soap and water. If virucidal agents such as povidone-iodine are available, they should be used for irrigation. Secondly, RIG should be administered, 20 IU/Kg of body weight. If feasible, the FULL DOSE should be administered (infiltrated) around the wound(s). If there is any remaining volume, it should be administered IM at a site distant from the vaccine administration site. To note, RIG should not be administered in the same syringe as the vaccine, and as it may suppress formation of antibody, it should not be administered in excess of the recommended dose. Lastly, HDCV should be administered in the same dosage as mentioned for pre-exposure prophylaxis.

The efficacy of the recommended prophylaxis is evidenced by the fact that of the millions of doses administered worldwide, there have been only 13 reported failures, and all of the failures have been associated with deviation from the recommended treatment protocol. The rate of systemic allergic reaction to the rabies vaccine is approximately 11 per 10,000 vaccinations, which has resulted in a few hospitalizations, but no deaths. It is currently the recommendation of the Advisory Committee on Immunization Practices (ACIP) that persons in high risk groups, such as veterinarians, animal handlers, and certain lab workers be treated with pre-exposure vaccine. Additionally, rabies prophylaxis is recommended that persons traveling (for more than 30 days) into areas where rabies is endemic and medical care is limited.(2,8). It is also recommended that even immunosuppressed patients receive prophylaxis if exposed to rabies. While pre-exposure prophylaxis is recommended, it is important to note that it does not negate the need for post-exposure. Pre-exposure prophylaxis negates the need for RIG immunization after exposure, but does not alter the remainder of the post-exposure prophylaxis schedule.

Far more effective than medical prophylaxis are the recommendations of the national working group on prevention and control of rabies in the United States. Their recommendations include:

1. Vaccinate all dogs and cats against rabies. Do not keep wild animals as pets.
2. Do not feed or pet stray animals; avoid animals you do not know.
3. Report any animals that are acting sick or strange to local animal control authorities.
4. Keep pets indoors at night. Feed pets indoors.
5. Keep pets fenced in or leashed.
6. Do not handle dead, sick, or injured wild animals. If necessary, use sticks or shovels and wear heavy gloves.
7. Remove roosting bats from homes and barns.
8. Keep all trash container lids tightly closed. Keep compost piles away from buildings.

Since the prognosis for patients displaying symptoms of rabies infection is invariably fatal, it is of the greatest importance for all possible measures to be taken to avoid the transmission of rabies, both through the application of animal vaccination and public health awareness. It is also vital for physicians to recognize individuals at risk for rabies exposure and treat them with both pre and post-exposure prophylaxis.

Questions

1. Which animals are most frequently reported rabid in the United States? (select all true answers)
    a. Squirrels
    b. Raccoons
    c. Rabbits
    d. Hamsters
    e. Skunks

2. Which of the following would provide the best method for ante-mortem diagnosis of rabies in a human?
    a. Identification of clinical symptoms.
    b. Direct fluorescent antibody testing.
    c. Identification of Negri bodies.
    d. Observation of the animal in question to be rabid.
    e. PCR of isolate from the saliva of the victim.

3. True/False: Inoculation of rabies from animal to human requires a physical animal-human contact.

4. In which of the following cases would post-exposure rabies prophylaxis be appropriate (select all appropriate):
    a. A tour group observes a large colony of bats emerge from a cave.
    b. While cleaning out the attic, a man removes a dead bat without using gloves.
    c. A child is bitten by his pet dog in Hawaii.
    d. A dead bat is removed from the crib of a child.

5. Which animal is most likely to transmit rabies to humans by mere contact (as opposed to a bite)?
    a. Bat
    b. Racoon
    c. Skunk
    d. Coyote
    e. Cat

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Answers to questions

1.b,e, 2.e, 3.False, 4.b,d, 5.a

Chapter VI.26. Rocky Mountain Spotted Fever
Douglas K. Kwock, MD

This is a 12 year old male who presented to the office 2 days ago with a 2 day history of fever, headaches, malaise, and generalized myalgias. He was diagnosed with a "viral syndrome" and given instructions for home symptomatic care. He is now in the emergency department with a rash that started on his hands and feet, spreading up his arms and legs. The fever, headaches, and myalgias have persisted. Mother states that today her son seems "out of it ".

Exam: VS T 40.2 C, P 100, R 26, BP 115/70. He is laying in a hospital gurney, awake and responsive, but tired and ill appearing. His skin has a maculopapular rash that blanches under pressure on the upper and lower extremities, including his palms and soles, and a few scattered macular lesions located on the upper trunk and back. There is a small 3mm round healed scab lesion on the left calf. His head is atraumatic and nontender. He has no mucosal (eye, nose, mouth, and throat) lesions. He does not exhibit any meningeal signs. His heart, lung, and abdominal exams are normal. There is tenderness to gentle palpation of his thigh and calf muscles. He is oriented and responds appropriately.

Laboratory studies reveal a normal white blood cell count that is slightly left shifted. He has a platelet count of 105,000. His serum sodium is 132mEq/L. Cerebrospinal fluid is normal.

The patient is asked about the scab on his calf. Four days prior to the onset of illness, while deer hunting with friends, he noticed an engorged tick on his calf. The tick was removed by "squeezing and scratching" causing a small abrasion that he soon forgot about. He is started in doxycycline. Rocky mountain spotted fever serologies are ordered on his blood.

Rocky mountain spotted fever (RMSF) is a tick-borne disease caused by the gram-negative intracellular bacterium Rickettsia rickettsii. It is the second most common tick transmitted disease in the United States. Among the rickettsial illnesses, it is the most common and severe in the United States (1).

The disease was first recognized in Idaho and Montana in the late 1800s and initially thought to be limited to the Rocky Mountain region. Today RMSF is seen in all geographic areas of the continental United States. Over half of reported cases are concentrated in the south-Atlantic and south-central regions. The highest rates of disease are reported in North Carolina and Oklahoma (2). Though historically significant, the "Rocky Mountain" moniker is misleading relative to the current disease epidemiology.

Males have a higher incidence of disease than females. RMSF is of pediatric concern because children <15 years of age account for the majority of infections with the highest incidence in children age 5 to 9 years (2).

The wood tick (Dermacentor andersoni) found in the Western and Rocky Mountain States and the dog tick (Dermacentor variabilis) found east of the Rocky Mountains are the primary hosts and vectors of R. rickettsii. Infected female ticks can transmit infection transovarially and lay infected eggs, perpetuating infection from generation to generation. Ticks can acquire the infection while feeding on an infected rickettsemic host. Tick nymph and larva stages primarily feed on small mammals. Adult ticks feed on large domestic mammals, including humans. Once a tick becomes infected, it will maintain the infection for life even across molting stages.

Cases can occur throughout the year but the majority (90%) occur during April through September (2). This seasonality correlates with periods of heightened outdoor human activity, and increased tick feeding activity amplifying the likelihood of exposure. Ticks transmit infection during a blood meal. Transmission usually occurs after the tick has been attached for a minimum of 6 to 10 hours. A history of tick bite or exposure to tick infested areas is often not recalled on initial evaluation and is obtained in only 60% of RMSF cases.

Prior to the advent of effective therapy, 30% of RMSF cases were fatal. Currently, the mortality rate is 2 to 4% despite available appropriate treatment (1). Poor outcome is usually the result of delayed diagnosis and the subsequent delay in initiating appropriate antimicrobial therapy (3).

The average incubation period of RMSF is 5 to 7 days (range 2 to 14 days). Early signs and symptoms of RMSF are nonspecific. Prominent features of RMSF are fever, headaches, myalgias, and malaise. The onset of fever is usually abrupt. Headaches in older patients are intense, persistent, and refractory to relief efforts. Gastrointestinal complaints (nausea, vomiting, abdominal pain) are common.

The most characteristic feature of RMSF is a rash that develops on days 2 to 4 of illness. It appears as a discrete macular or maculopapular rash that blanches with pressure. The ankles and wrists are initially involved. Rash on the palms and soles is characteristic of RMSF. The rash spreads proximally up the arms and legs and eventually involves the trunk. Petechial and hemorrhagic lesions develop giving the classic "spotted" appearance of the illness. However, there have been reports of "spotless" or "almost spotless" RMSF illnesses. During convalescence, desquamation may occur in the most affected skin areas.

Fever, rash, and a history of tick bite comprise the "classic triad" of RMSF. This triad is seen in two-thirds of patients. Because the rash typically appears late in the course of illness, the classic triad is rarely useful in assisting with an early diagnosis which is critical to successful management.

Central nervous system involvement may develop in severe RMSF with symptoms of disorientation, meningismus, seizures, and coma. Cardiac complications include arrhythmias and congestive heart failure. Other less frequent signs and symptoms are pneumonitis, hepatosplenomegaly, edema, and conjunctivitis (4).

The initial presentation of RMSF is nonspecific and can mimic any generalized febrile illness. The maculopapular rash of measles and non-polio enteroviruses can resemble the rash of RMSF. A petechial rash necessitates the consideration of meningococcemia or septic shock (staphylococcus or streptococcus). Ehrlichiosis shares many similar features with RMSF.

There is no laboratory test that definitively diagnoses RMSF in the early phase of illness. Thus, an early diagnosis depends on a high index of suspicion, a compelling clinical presentation, and suggestive ancillary laboratory data.

The CBC WBC may be high, normal, or low but is usually left shifted. Thrombocytopenia is common in RMSF. Mild thrombocytopenia is probably related to platelet adherence to affected endothelial cells. Severe thrombocytopenia usually represents a consumptive coagulopathy. Hyponatremia is common. CSF is usually normal but may demonstrate a mild pleocytosis.

Diagnosis is made by serologic studies. The most sensitive and specific tests are indirect immunofluorescent antibody (IFA), enzyme immunoassay (EIA), and compliment fixation (CF). Other available serologic studies are latex agglutination (LA), indirect hemagglutination (IHA), and microagglutination (MA). Antibodies can be detected 7 to 10 days from disease onset. A single serum IFA titer of 1:64, CF titer of 1:16, or LA, IHA, or MA titer of 1:128, are highly suggestive of RMSF. A 4-fold rise between acute and convalescent antibody titers is diagnostic (5).

Early treatment is necessary and often empiric based on index of suspicion considering history, clinical course, and epidemiology. Treatment should not be withheld until a definitive diagnosis is made. Delay in initiating treatment leads to a poorer prognosis. Without treatment, RMSF can be fatal. Chloramphenicol, tetracycline, and doxycycline are effective against R. rickettsii. Doxycycline is the drug of choice for treatment of RMSF in patients of any age. Historically, chloramphenicol was recommended for children <8 years of age. Tetracycline and doxycycline were not favored because they bind to calcium of developing teeth and bones causing permanent discoloration. However, there are several reasons why doxycycline is the recommended first-line therapy. It does not bind to calcium as readily as tetracycline. A single course of doxycycline treatment carries little risk of teeth staining. Chloramphenicol has been associated with the development of irreversible aplastic anemia, and has been shown to be less effective than doxycycline for treatment of RMSF (2). Doxycycline is also active against ehrlichiosis, which may be clinically indistinguishable from RMSF. The efficacy of chloramphenicol in ehrlichiosis has not been established. Doxycycline is given at a dose of 2 to 4 mg/kg/day, divided every 12 hours, with a maximum dose of 200mg/day. The dose is the same regardless of oral or intravenous administration. Duration of therapy is for a minimum of 5 to 7 days and until the patient has been afebrile for at least 48 hours (5).

Limiting exposure to ticks is the most effective method of decreasing the risk of disease. If tick exposure is anticipated, there are several suggested means of protection. Clothing should cover a maximal amount of surface area to minimize exposed skin and should be light-colored allowing easy tick detection. Long pants should be tucked into socks or boots. Tick or insect repellants should be applied to clothing and exposed skin. Thorough body checks should be performed after exposure to a tick infested area. Particular attention should be paid to the head and scalp where ticks may be difficult to find. Proper skin removal of ticks is important in decreasing the risk of infection. Squeezing, crushing, pinching, or the folk remedy of burning the tick with a cigarette may actually facilitate rickettsiae transmission. The tick should be removed with a fine-tipped tweezer grasped as close to the skin as possible and pulled upward with a slow steady pressure. The skin site should be cleaned and disinfected. If possible, the tick should be saved for identification if illness develops.

There is no licensed vaccination for prevention of RMSF. Prophylactic therapy for asymptomatic individuals with a recent tick bite or exposure to a tick infested area is not recommended.

Full recovery is the rule with administration of appropriate antibiotics within 5 days of disease onset. Fulminant fatal RMSF has been associated with glucose-6-phosphate dehydrogenase (G6PD) deficiency (6), possibly related to increased hemolysis due to infection.

Questions

1. True/False: RMSF is most prevalent in the Rocky Mountain states.

2. True/False: RMSF can be "ruled out" based on a lack of history of tick bite.

3. True/False: Treatment of RMSF is often empiric.

4. True/False: Rash typically starts on the trunk and spreads distally.

5. Which is the preferred method of removing an attached tick?
   a. Use a lit match or cigarette to burn the tick stimulating it to detach and flee.
   b. Gently pinch the body of the tick with fingers and lift straight off.
   c. Use fine-tipped tweezers to grasp the tick as close to the skin as possible and pull upward with slow steady pressure.
   d. Apply petroleum jelly (Vaseline) over the tick and wait for the tick to suffocate or detach for air.
   e. Don't remove, leave the tick alone.

6. Which of the following is NOT a recommended means of RMSF prevention?
   a. Insect or tick repellants to clothing and exposed skin.
   b. Prophylactic doxycycline prior to exposure to tick infested areas.
   c. Minimize exposed skin with light [Note spelling change]-colored clothing.
   d. Avoid known tick infested areas.
   e. Survey skin and scalp after exposure to tick infested areas.

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Answers to questions

1. False. Primarily south-Atlantic and south-central states.

2. False. A history of tick bite or exposure is obtained in only 60% of cases.

3. True. Therapy should never be withheld until a definitive diagnosis is made. Poorer outcome with increased mortality is associated with delay in initiating treatment.

4. False. Rash typically starts on the hands/wrists and feet/ankles. Involvement of the palms and soles is classic.

5.c, 6.b

Chapter VI.27. Lyme Disease
Judy Makowski Vincent, MD

A 7 year old boy is brought to the pediatric clinic in August with the chief complaint of a large, red circular rash on his left thigh. The rash has been present for 2 weeks and has been enlarging. His father states that 3 weeks ago, the family was visiting relatives at a rural farm in Connecticut, and one day after playing outside in the woods, the boy was found to have a tick attached to his thigh. His father had removed the tick with tweezers; however a red macule remained at the site where the tick had been attached. One week after the tick was removed, a red ring developed around the macule, and then the ring appeared to grow larger by expanding outward, leaving an area of central clearing. The boy has had a mild headache and myalgia, but has been afebrile.

Exam: VS T 37.1, P 90, RR 20, BP 100/70. He is alert, active, in no distress, and is non-toxic. Over the anterior surface of his left thigh, there is a red ring, 20 cm in diameter, with central clearing, and a central brownish-red macule that is 3 mm in diameter. The thigh is non-tender. All joints are non-tender and non-swollen. His neck is supple without lymphadenopathy. The remainder of his exam is unremarkable.

No laboratory tests are performed. The skin lesion is diagnosed as erythema migrans (EM), and a diagnosis of Lyme disease is made. He is judged to have early localized infection. He is treated with amoxicillin, 50 mg/kg/day po divided tid for 21 days. His headache and myalgia resolve within one week, and the EM resolves completely by the end of amoxicillin treatment.

A zoonosis is a disease of animals that may be transmitted to man. A vector is a carrier that transfers an infectious agent from one host to another. Lyme disease is the most common vector-borne zoonosis in the United States and is caused by the spirochete Borrelia burgdorferi. It is a multisystem, multistage, inflammatory illness affecting primarily the skin, nervous system, heart and joints. If you have difficulty remembering this, note that these affected systems are identical to those affected in rheumatic fever.

Lyme disease was recognized as a distinct disease in 1977 after a group of children in Old Lyme, Connecticut was diagnosed as having "juvenile rheumatoid arthritis". Two mothers of children with arthritis contacted the Connecticut State Department of Health and reported the occurrence of arthritis in 12 children in Old Lyme; of these, 4 lived on the same street. The mothers also reported arthritis in several members of their families and in families living in the neighboring towns of Lyme and East Haddam. An epidemiologic investigation was begun and has resulted in the knowledge of Lyme disease today.

B. burgdorferi is transmitted to humans by the ticks of the Ixodes ricinus complex. I. scapularis (the black-legged or deer tick) is the vector in the eastern United States, while I. pacificus (the western black-legged tick), transmits B. burgdorferi in the western United States (1). In the spring, the adult ticks lay eggs, from which larvae emerge. On the east coast of the United States, the larvae become infected when they feed on the reservoir, the asymptomatically-spirochetemic white-footed mouse. Since the spirochete infection is not transmitted from mother tick to their eggs, the tick larvae are not infected until they feed on this mouse. On the west coast, Lyme disease occurs sporadically, due to the fact that I. pacificus larvae feed more often on non-spirochetemic lizards than on white-footed mice (1). In the nymphal stage, the ticks feed predominantly in the spring and early summer, and two-thirds of cases of Lyme disease cases are reported from July to October. It is the nymphal stage that transmits the infection most often to humans. Since the nymphs are small, they often go undetected. The adult tick survives the winter by attaching to a host mammal, which is not involved in the life cycle of the spirochete, but merely allows the tick to survive over the winter (1). If white-tailed deer live in the environment, they are the host of choice; however at least 30 types of wild mammals and 49 species of birds may be host to the tick (2).

The number of cases reported annually has increased approximately 25-fold since national surveillance was begun in 1982 (1). During 1993-1997, a mean of 12,451 cases were reported by states annually to CDC. In the United States, the disease is primarily localized to states in the northeastern, mid-Atlantic, and upper north-central regions, and to several areas in northwestern California. Most cases of Lyme disease result from exposure to infected ticks during activities such as property maintenance, recreation, and leisure activity. Therefore persons who live or work in wooded areas or areas with overgrown brush infested with vector ticks are at risk for acquiring Lyme disease.

The B. burgdorferi spirochete is transmitted by infected ticks, which transmit the organism into the blood vessels in the skin of its host. The tick must attach to the host for 48 to 72 hours for the risk of transmission of B. burgdorferi to become substantial (3). The majority of patients with Lyme disease do not recall a tick bite, which means that with an unrecognized tick bite, these individuals are at greater risk to acquire Lyme disease, because unrecognized ticks may feed longer (3).

The incubation period from infection to onset of symptoms is 7 to 14 days, with a range of 3 to 30 days. B. burgdorferi spreads locally into the skin from the site of the tick bite, which results in a single EM lesion in approximately two-thirds of patients who become symptomatic. Days to weeks later, the spirochete may disseminate via lymphatic or blood-borne routes to other areas of the skin, causing multiple EM lesions, and to the eye, muscle, bone, synovial tissue, central nervous system and heart (2,3,4).

Lyme disease occurs in stages, and this is useful to remember when considering the diagnosis (2,3,4). The stages are: early localized (stage 1); early disseminated (stage 2); and late disseminated (stage 3).

Early localized infection (stage 1) occurs 3 to 32 days after the tick bite (3). It usually manifests as the characteristic EM rash, and may be accompanied by fever, malaise, headache, fatigue, myalgia, and arthralgia. EM by itself is diagnostic of Lyme disease, and a positive Lyme serology is not required. Indeed, most patients have negative serology in this stage (3). Thirty to fifty per cent of persons with evidence of recent infection are asymptomatic (3). The rash is usually annular, spreading from a central lesion, which is the tick bite. It may be solidly erythematous, may be a target lesion, or may have a vesicular or necrotic center. The rash may be pruritic, painful, or asymptomatic. Without treatment, the rash expands in size; hence the name migrans. The average size is 15 cm, however the lesions may be as large as 30 cm in diameter (4). A patient may have multiple EM lesions.

Early disseminated infection (stage 2) begins 3-10 weeks after the appearance of the EM lesion (3,4). Patients may develop secondary EM lesions which are not at the site of the tick bite. These lesions are often accompanied by the same systemic symptoms as primary EM. Focal neurologic involvement, the most common of which is isolated seventh cranial nerve or (Bell's palsy), is also a manifestation of early disseminated disease. This may be the presenting, as well as the only, manifestation of Lyme disease and is relatively common, affecting about 3% of children (3). Antibiotic treatment has no effect on the clinical course of the Bell's palsy, which completely resolves in 2 to 8 weeks. Lyme-related Bell's palsy should not be treated with corticosteroids (3). Other complications in stage 2 may be aseptic meningitis, carditis, radiculoneuropathy, lymphadenopathy, conjunctivitis, neck pain, fever, headache, arthralgia, myalgia, and fatigue. Radiculoneuropathy is more common in European adults, but is also seen in children in the United States (3,4).

If the patient is untreated or is inadequately treated, late-disseminated (stage 3) Lyme disease may develop 2 to 12 months after the tick bite (2,3,4). The most common manifestation of late disseminated Lyme disease in children is arthritis. Large joints are affected most often, with the knee being involved in >90% of cases (3). The involved joint is tender, erythematous and swollen; however the clinical findings are not as marked as in bacterial arthritis. With treatment, the joint shows signs of improvement in 4 to 7 days, with complete resolution in 2 to 6 weeks. Occasionally symptoms will recur after treatment, requiring another course of antibiotics. Chronic arthritis occurs primarily in patients with DR-2, DR-3, or DR-4 HLA types (2).

The most common mistake in diagnosis, is the overdiagnosis of Lyme disease by obtaining Lyme serology in patients who have vague, nonspecific symptoms, but who do not have risk factors for Lyme disease (i.e., patients who do not live or work in heavily wooded areas or areas that have dense underbrush infested with vector ticks and who do not have frequent or prolonged exposure to tick-infested habitats) (5). The ELISA serologic test for Lyme disease has high sensitivity but low specificity, and positive results in patients at low risk of disease are likely to be false positive results. At this time, diagnostic tests, including the polymerase chain reaction, based on the identification of antigens or DNA of B. burgdorferi lack sufficient specificity or sensitivity to be clinically useful (3).

Early and uncomplicated infections in children and adolescents usually respond well to orally administered antibiotics (3,4,6). Treatment of Lyme disease is outlined in Table 1. Parenteral antibiotics are generally recommended for treating meningitis, carditis, later-stage neurologic Lyme disease, and complicated Lyme disease arthritis. Late, complicated Lyme disease may respond slowly or incompletely, and more than one antibiotic treatment course may be required to eliminate active infection (2).

Table 1. Treatment of Lyme Disease (3)

Stage 1 - Early localized disease (EM):

Children <9 years old: amoxicillin, 50 mg/kg/day po divided tid (maximum dose 500 mg/dose) for 21days.

Children ≥9 years old: doxycycline, 100 mg po bid for 21 days. Alternatives for those who cannot take amoxicillin or doxycycline include: cefuroxime axetil, 30-50 mg/kg/day po divided bid (maximum dose 500 mg/dose) for 21 days, or erythromycin, 30-50 mg/kg/day po divided qid (maximum dose 250 mg/dose) for 21 days.

Stage 2 - Early disseminated disease:

Uncomplicated: Treat as for EM

Bell's palsy or other cranial nerve palsy: Treat as for EM, but for 21-30 days. Do not use corticosteroids.

Carditis: Treat as for late neurologic disease.

Meningitis: Treat as for late neurologic disease

Stage 3 - Disseminated disease:

Neurologic disease with isolated cranial nerve palsy: Treat as for EM but for 21-30 days.

Other: ceftriaxone 50-80 mg/kg/day in a single dose (maximum dose 2 g) for 14-21 days IV or IM; or penicillin G, 200,000-400,000 units/kg/day (maximum 20 million units/day) divided q 4 hrs, for 14-21 days IV.

Arthritis: Initial treatment same as for EM except treat for 30 days. If symptoms recur or fail to resolve after 2 months, then treat as for late neurologic disease. Some experts give a second course of oral antibiotics before using a parenteral agent.

The prognosis for Lyme disease in children and adolescents is excellent. Gerber et al. (6) reported a prospective, longitudinal, community-based cohort study of children with Lyme disease in southeastern Connecticut which studied 201 children enrolled over a period of 20 months, with a mean age of 7 years and a range of 1 to 21 years. All but 3 of the 201 patients were treated for 2 to 4 weeks with conventional antibiotic therapy, which was administered orally in 96% of cases. All had prompt clinical responses. After 4 weeks, 94% were completely asymptomatic. At follow-up, a mean 25.4 months later, none of the patients had evidence of either chronic or recurrent Lyme disease. Six patients subsequently had a new episode of EM. No patient progressed from early to late disease.

Parents may fear that their children and adolescents will acquire complications from Lyme disease that are debilitating, chronic, or fatal (6). They may question whether orally administered antimicrobials can be as effective as intravenously administered antimicrobials. In addition, if a child or adolescent later has vague, nonspecific symptoms after completing an appropriate course of antimicrobials, parents often worry that the antimicrobial therapy has been inadequate and request that additional antimicrobial therapy be prescribed. The information gathered by Gerber et al. can be used to reassure parents that Lyme disease in children and adolescents has an excellent prognosis and responds well to appropriate antimicrobial therapy.

Prevention is best achieved by avoidance of tick habitats. Whenever possible, persons should avoid areas that are likely to be infested with ticks, particularly in spring and summer when nymphal ticks feed. Ticks favor a moist, shaded environment, especially that provided by leaf litter and low-lying vegetation in wooded, brushy or overgrown grassy habitats (1).

Persons who are exposed to tick-infested areas should wear light-colored clothing so that ticks can be spotted more easily and removed before becoming attached. Wearing long-sleeved shirts and tucking pants into socks or boot tops can help keep ticks from reaching the skin. Applying insect repellents containing DEET (n,n-diethyl-m-toluamide) to clothes and exposed skin, and applying permethrin, which kills ticks on contact, to clothes, should also help reduce the risk of tick attachment. Because transmission of B. burgdorferi from an infected tick is unlikely to occur before 36 hours of tick attachment, daily checks for ticks and their prompt removal will help prevent infection (1).

The number of ticks in endemic residential areas can be reduced by removing leaf litter, brush, and woodpiles around houses and at the edges of yards, and by trees and brush to admit more sunlight, thus reducing deer, rodent, and tick habitats. Tick populations have also been reduced by applying pesticides to residential properties.

In general, antibiotic prophylaxis after a tick bite is not recommended. Persons who are bitten by a deer tick should remove the tick and seek medical attention if any of the signs and symptoms of Lyme disease develop (1,4).

A vaccine consisting of recombinant B. burgdorferi outer-surface lipoprotein A (OspA) with adjuvant (LYMErix) was licensed by the U.S. Food and Drug Administration for use in the United States in 1998. A placebo-controlled trial of the vaccine revealed that pain at the injection site was the most common side effect, reported by 24% of vaccine recipients vs. 8% of controls (7). The efficacy of the vaccine in protecting against symptomatic Lyme disease was 49% in the first year (after the first 2 doses) and 76% in the second year (after the third dose). Vaccine efficacy in preventing asymptomatic B. burgdorferi infection was 83% in the first year and 100% in the second year (7).

The cost effectiveness of vaccinating against Lyme disease has been analyzed by Meltzer et al. (8). A single answer regarding the cost effectiveness of vaccinating a person against Lyme disease cannot be calculated. The tables and figures in the study by Meltzer et al., also reprinted in the MMWR (1), will assist physicians, health care decision makers, and public health authorities to determine the cost effectiveness of vaccination for their specific situations.

Assessing the risk for Lyme disease (1) This is primarily determined by the following:

1. Density of vector ticks in the environment, which varies by place and season.
2. Prevalence of B. burgdorferi infection in vector ticks.
3. Extent of person-tick contact, which is related to the type, frequency, and duration of a person's activities in a tick-infested environment.

Questions

1. True/False: Over 90% of children with Lyme disease can be treated successfully with oral antibiotics.
2. True/False: Children with Bell's palsy should be treated with corticosteroids.
3. True/False: Multiple EM lesions are a sign of late disseminated Lyme disease.
4. True/False: Lyme vaccine is recommended for persons aged 15-70 years whose exposure to a tick-infested habitat is frequent and prolonged.
5. True/False: If a patient has an EM lesion, a diagnosis of Lyme disease can, and should, be made without serologic testing.
6. True/False: Most patients with Lyme disease do not recall having had a tick bite.
7. True/False: Patients with uncomplicated early disseminated disease should receive 30 days of antibiotics.
8. True/False: Lyme vaccine is a live-virus vaccine.
9. True/False: Lyme disease occurs most commonly in spring and summer, when nymphal ticks feed.
10. True/False: Lyme serology is so highly specific that positive results always predict the presence of Lyme disease, even in patients at low risk for the disease.
11. True/False: The number of cases reported annually has increased approximately 25-fold since national surveillance was begun in 1982.

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Answers to questions

1. True.
2. False. Bell's palsy due to Lyme disease should NOT be treated with corticosteroids.
3. False.
4. True.
5. True.
6. True.
7. False.
8. False.
9. True.
10. False. Positive Lyme serology in low risk cases are usually false positives.
11. True

Chapter VI.28. Leptospirosis
Selina S.P. Chen, MD, MPH

A 14 year old male, previously healthy, presents to the emergency department with a one week history of fever, malaise, abdominal discomfort, calf pain and a mild sore throat. He denies any cough, hemoptysis, dyspnea, chills, night sweats, anorexia, nausea, vomiting, or dysuria. His urine output is good. There is no history of trauma, blood transfusions, or recent travel.

He lives with his parents. His father is a fisherman and his mother is a housewife. He is in the 9th grade with a 3.1 GPA. He is the captain of the school swim team. He also swims in streams and canals. He denies substance abuse and sexual activity.

Exam: VS T 38.4C, P 110, RR 18, BP 130/80 mm Hg. Height and weight are at the 50th percentile. He is alert in no acute distress. He is noted to have a moderate conjunctival suffusion (redness of the conjunctiva), with scleral icterus. His pharynx is injected, but his tonsils are not enlarged. His neck is supple with 1 cm anterior lymphadenopathy. Heart is regular with no murmur. His lungs are clear. His abdomen has normoactive bowel sounds with tender hepatomegaly; but no rebound or guarding. His extremity muscle strength is 4/5. His lower extremity muscles are tender to palpation. Homans sign is negative. No nodules are palpable.

Labs: WBC 9,000 with 80% polymorphonuclear leukocytes, hemoglobin 14 g/dL, platelet count 60,000. Coagulation times are normal. BUN 70 mg/dL, creatinine 3 mg/dL, total bilirubin 10 mg/dL, direct bilirubin 8 mg/dL, AST 80 UI/L, ALT 70 U/L. CPK 1,800 UI/L. UA shows ketones >160mg/dL, >100 red blood cells per high-powered field. No pyuria, organisms or casts are seen on UA. Chest and abdominal radiographs are normal.

He is admitted to the hospital and started on IV penicillin empirically for possible leptospirosis. Culture and serology studies are pending.

Leptospirosis (from Greek leptos, meaning "fine," and speira, meaning "a coil") is a zoonosis, which was first discovered as a disease of sewer workers by Landouzy in 1883. However, Adolf Weil of Heidelberg reported the clinical entity of fever, jaundice, hemorrhage, and renal failure in 1886. The causative organism was independently isolated in 1915 by German and Japanese investigators. The cause of many diseases was then discovered to be due to leptospira species. These diseases include pretibial fever, swineherd's disease, canefield fever in Australia, seven-day fever in Japan, swamp or mud fever in Europe, and Fort Bragg fever in the United States. The same Japanese investigators shortly discovered the role of rats as carriers. Rats are the most common reservoirs; however, many mammals have since been identified as reservoirs, especially cattle and feral pigs in Hawaii. Spread of leptospirosis can occur by contact with urine, blood or tissues from infected persons. The organisms enter the body through breaks in the skin or through mucous membranes. Infection is commonly acquired by bathing in contaminated water or by drinking contaminated water.

Leptospirosis presents with great clinical variability from a mild flu-like illness to an acute life-threatening condition, known as Weil's syndrome. Two major clinically recognizable syndromes are observed: anicteric leptospirosis (90%) and the more severe and potentially lethal form, icteric leptospirosis or Weil's syndrome (10%). The incubation period lasts 1-2 weeks.

Each syndrome has two distinct phases: the septic phase and the immune phase. The septic phase lasts 4-7 days, consisting of a flu-like syndrome. Leptospira can be found in the bloodstream and cerebral fluid. The immune phase lasts 4-30 days, consisting of aseptic meningitis, uveitis, iritis, rash, hepatic, and renal involvement. Leptospira can then be found in the urine and aqueous humor.

In anicteric leptospirosis, the septic phase is characterized by fever, headache, abdominal pain, anorexia, nausea, vomiting, and myalgia. The most common physical finding is conjunctival suffusion (reddening of the eye surface) without purulent discharge. Other signs include maculopapular skin rashes, pharyngeal injection, lymphadenopathy, hepatomegaly, and splenomegaly. The immune phase is characterized by less prominent fever, more intense headache, aseptic meningitis, conjunctival suffusion, uveitis, hepatosplenomegaly, rash, and pulmonary involvement.

Icteric leptospirosis, previously known as Weil's syndrome, is a more serious and potentially fatal syndrome. The septic and immune phases are not as distinct. The septic phase resembles anicteric leptospirosis. The immune phase is characterized with hepatorenal and vascular dysfunction. Jaundice and azotemia may develop.

Most cases of leptospirosis are self-limited, but complications include uveitis, renal failure, hemorrhage, DIC, acute respiratory distress syndrome, myocarditis, and rhabdomyolysis. Liver failure is generally reversible. In the absence of jaundice, the disease is rarely fatal. Oliguria is the only independent factor which adds to mortality risk. Other risk factors include dyspnea, alveolar infiltrates on chest radiography, repolarization abnormalities on electrocardiogram, and leukocytosis. Deaths have been attributed to myocarditis, irreversible septic shock, acute respiratory failure, and multiple organ failure.

Routine laboratory findings in leptospirosis are often non-diagnostic. CBC often reveals normal leukocyte counts (usually <10,000, but may range between 3,000 to 26,000), with neutrophilia in two-thirds of patients, and an elevated erythrocyte sedimentation rate. Anemia occurs with later presentations. Thrombocytopenia is seen most commonly in patients with azotemia. Urinalysis may show microscopic hematuria, proteinuria, pyuria, and granular casts. Aseptic meningitis is the hallmark presentation of the immune stage of anicteric leptospirosis. CSF examination shows a pleocytosis (<500) with an early neutrophilic or lymphocytic and late mononuclear cell predominance, normal glucose, and mildly elevated protein (50-110 mg/dL).

Jaundice is only observed in patients with Weil's syndrome. These patients can develop hepatic and renal dysfunction and hemorrhage. Serum bilirubin is usually <20 mg/dL, but can reach up to 60-80 mg/dL, predominantly as conjugated bilirubin. Liver function test can be elevated twofold to threefold. Hypoprothrombinemia occurs in a minority of patients. Myositis with elevated creatinine phosphokinase occurs in half of the patients.

Chest radiographs may reveal small nodular densities that can progress to infiltrates or consolidation. Pathologically, infiltrates are caused by hemorrhagic pneumonitis.

The diagnosis of leptospirosis is confirmed by isolation of the organism from any clinical specimen or seroconversion or fourfold increase in antibody titers. Leptospira can be cultured with special media from blood or CSF in the first 10 days and urine cultures are positive during the second week of illness and remain positive for up to 30 days after the resolution of symptoms. Growth in culture requires special semisolid, protein-supplemental media and takes at least one week (up to three months). Therefore, the diagnosis is made more frequently by serologic testing. A number of serologic tests are employed including micro-agglutination test (MAT), macroscopic agglutination test, indirect hemagglutination, and ELISA. Although MAT is considered the gold standard, it is not readily available in many institutions. ELISA is typically first performed and if suggestive, MAT can then be sent to the CDC in Atlanta. Newer studies utilizing polymerase chain reaction (PCR) are being investigated.

Differential diagnoses include dengue fever, hemorrhagic yellow fever, malaria, influenza, Louse-borne epidemic relapsing fever, tick-borne endemic relapsing fever, arthropod-borne and rodent-borne pathogens. Although dropped from the list of national notifiable diseases since 1994, leptospirosis remains a reportable illness in Hawaii.

Penicillin or tetracycline-based antibiotics, preferably doxycycline, are the antibiotics of choice even when treatment is delayed. In less ill patients, an oral dose of doxycycline for one week shortens the course of early leptospirosis. Intravenous penicillin used in severely ill patients reduces the duration of fever and renal dysfunction. In the most severe forms, patients must be admitted to an ICU for supportive therapy and close observation. Close monitoring and management of electrolytes, dehydration, hypotension, and hemorrhage are the mainstay of therapy. Although renal failure often resolves spontaneously, some patients may require temporary hemodialysis. Administration of vitamin K can help correct hypoprothrombinemia.

Doxycycline can prevent infection; however, exposure is difficult to predict. Prevention is best accomplished by effective rat control and avoidance of known contaminated water sources or infected urine.

Questions

1. The most specific physical finding of leptospirosis include:
    a. fever
    b. conjunctival suffusion
    c. renal failure
    d. myalgia

2. More characteristic findings in the immune phase of anicteric leptospirosis include:
    a. fever
    b. jaundice
    c. renal failure
    d. aseptic meningitis

3. Good prognostic factors for the patient in our case include all of the following, except:
    a. good urine output
    b. normal leukocytes
    c. normal coagulation tests
    d. no infiltrates on chest radiography

4. Leptospira are best cultured from:
    a. blood
    b. plasma
    c. urine
    d. CSF
    e. none of the above

5. Therapy of leptospirosis may include all of the following except:
    a. alkalinization of urine
    b. supportive therapy
    c. doxycycline
    d. penicillin

6. Which clinical factor best distinguishes the life threatening form of leptospirosis from the more common self-limited form of leptospirosis?
    a. azotemia
    b. pneumonia
    c. meningitis
    d. dehydration
    e. jaundice

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Answers to questions

1.b, 2.d, 3.c

4.e. None of the above. Leptospira are difficult to culture. Culture requires special laboratory techniques not available at most clinical labs. Thus, the diagnosis is usually confirmed by serology.

5.a

6.e. Jaundice indicates icteric leptospirosis, which is a more serious condition which has a higher mortality rate. Azotemia is an additional marker of severity.

Chapter VI.29. Cat Scratch Disease
Judy Makowski Vincent, MD

A four year old girl presents to the pediatric clinic with a chief complaint of a slowly enlarging mass in her right armpit for the past two weeks. She has had no fever, but has had some loss of appetite. The mass was initially small and did not hurt; however, it has now grown to the size of an orange and has become painful. She cannot lower her arm due to the pain from the mass, and she carries her arm extended at 90 degrees to her body. Movement of her arm exacerbates the pain. She does have a 3 month old kitten at home that she "rescued from a sewer". It was covered with fleas when she found it. It playfully bites and scratches her. Three weeks ago it scratched her right thumb. The scratch healed, but a small "wart" has developed in the line of the scratch. There is a scab on the wart and her mother has tried to squeeze the wart, but no pus has come out.

ROS: Non-contributory. No cough. No weight loss. No change in activity other than being unable to use her right arm well.

Exam: VS T 37.2, RR 18, P 102, BP 100/60. She is alert and very cooperative. HEENT is negative. Neck is supple without adenopathy. Chest is clear. Heart regular without murmur. Abdomen exam is normal without hepatosplenomegaly. Neurologic exam is normal (mental status, gait, strength, and reflexes). Her right axilla reveals an 8x8 cm firm, tender, mobile, warm, non-erythematous, non-fluctuant mass that is consistent with an enlarged axillary lymph node. Her right thumb has a 1 cm linear, non-inflamed, healing scar that is consistent with a kitten scratch. In the middle of the linear scar, there is a 3 mm brownish-red papule with a small central crust.

Lab: CBC WBC 8.0, 62% segs, 10% bands. Ultrasonography of the mass reveals that it is a matted group of about 5 lymph nodes which are mostly solid in appearance. There is evidence of a small amount of necrosis at the periphery of one of the lymph nodes.

Impression: Lymphadenopathy due to cat scratch disease.

Clinical course: Because the axillary node is enlarged and painful, you elect to treat her with oral azithromycin at a dose of 10 mg/kg/day for the first day and 5 mg/kg/day for the next 4 days. Serology for Bartonella henselae is obtained, and the result returns one week later with an IgG of 1:512 (a positive result is a value greater than 1:64). The node remains the same size for a week and then begins to get smaller. The adenopathy resolves in one month.

It is now known that cat scratch disease (CSD) is a multisystem disease caused by a small Gram negative bacillus named Bartonella henselae, formerly known as Rochalimaea henselae. As early as 1932, physicians in the United States recognized patients with CSD, but the cause of the disease eluded detection until 1983 when researchers at the Armed Forces Institute of Pathology at Walter Reed Army Medical Center in Washington, D.C. detected the organism in lymph node tissue from patients with clinical CSD. Identification of the causative organism has allowed researchers to identify the epidemiology and transmission of the disease, identify atypical forms of CSD, develop serologic diagnostic tests, and perform placebo-controlled treatment trials.

Jameson et al, recently reported the results of a survey of 33 geographic regions throughout North America and showed that increasing prevalence of antibody to B. henselae in cats paralleled increasing climatic warmth and annual precipitation (1). Seroprevalence was highest in regions with warm humid climates which also have a higher incidence and degree of cat flea infestation. The southeastern United States, Hawaii, coastal California, the Pacific Northwest and the south central plains had the highest average B. henselae antibody prevalences. Alaska, the Rocky Mountains-Great Plains region, and the Midwest had the lowest average B. henselae antibody prevalences.

CSD is generally a benign, self-limited disease in immunocompetent hosts. Although CSD may be associated with significant morbidity, no deaths have been reported in immunocompetent persons with typical CSD proven by positive skin test, positive serology, or by DNA testing (2). Deaths have been reported rarely in immunocompromised patients. Several members of a family may develop clinical CSD, whereas some have asymptomatic infection as evidenced by development of B. henselae antibody. Infection appears to confer lifelong immunity, because reports of recurrences of clinical CSD are rare (2).

B. henselae bacteremia occurs in flea-infested well appearing kittens usually less than one year old, and less commonly in older cats. The organism is transmitted among cats by the cat flea. It is transmitted to humans by a cat scratch, bite or other intimate contact. The pathologic response to infection with B. henselae varies significantly with the status of the host immune system. In immunocompetent hosts, the response is granulomatous and suppurative. In immunocompromised hosts, the response is vasculoproliferative (2).

Organisms are not seen in routinely stained tissue preparations. In Warthin-Starry or Brown-Hopp's tissue-stained CSD lymph node preparations, Gram negative argyrophilic (i.e., it takes up silver stains, so it shows up better with silver staining) non-acid-fast, pleomorphic bacilli may be seen in the tissues. The bacilli are very small and are seen primarily in the walls of blood vessels, in macrophages lining the sinuses, in or near germinal centers, and in microabscesses. Here they may appear as single organisms, or in chains, or clumps.

B. henselae may be grown in standard microbiology laboratories by plating the sample (patient's lymph node aspirate or blood from suspected-bacteremic kittens) directly onto chocolate agar, then streaked and incubated under 6% CO2 at 35 degrees C for 60 days. The organism is fastidious in its growth. Therefore the plates should be left in the CO2 incubator and not examined or exposed to room air for the first 14 days. After 14 days, B. henselae manifests as grayish-yellow pinpoint-sized colonies that are best seen when the plate is held tangentially to the light. If no growth occurs within 60 days, the results may be interpreted as negative.

CSD occurs as both typical and atypical disease (2). Typical CSD in an immunocompetent host is manifested by a characteristic and highly predictable clinical course. In nearly all cases, patients give a history of a scratch, bite, contact or intimate association with a cat, most often a newly acquired kitten. In some patients, a round, red-brown, nontender papule develops in the scratch line after 3 to 10 days. It may vary in size from 1 to several millimeters and may persist for only a few days or for as long as 2 to 3 weeks. In the next 1 to 2 weeks, one or more regional lymph nodes gradually enlarge. The most commonly involved lymph nodes are the anterior cervical, axillary, inguinal, femoral, preauricular, supraclavicular, and epitrochlear nodes; however any node can be involved if it is in the path of lymphatic drainage from a site that has been inoculated with B. henselae.

CSD lymph nodes tend to be large with an average diameter of 4 to 6 cm at the time of maximum size, but can be as large as 10 to 13 cm. After 1 to 2 weeks of growth, they remain the same size for 2 to 3 weeks and then resolve over an additional period of 2 to 3 weeks, with the usual course of the disease lasting for 2 to 3 months. Some cases are more severe and more protracted, lasting up to 6 to 7 months. Although most of the nodes are moderately tender, some are nontender. Most patients with typical CSD remain afebrile and are not ill-appearing. Some patients experience anorexia, malaise, headache, arthralgia, and abdominal, neck, back or extremity pain.

A very useful clinical feature that distinguishes CSD from acute pyogenic lymphadenopathy, is that CSD lymphadenopathy only rarely develops overnight. In our experience, most patients with CSD tend to seek medical care after lymphadenopathy has been present

for 7 to 14 days. In contrast, most patients with acute pyogenic adenopathy present for care within 24 hours of onset of the adenopathy. CSD lymphadenopathy is unilateral and isolated to a regional group of lymph nodes in immunocompetent patients. Therefore, if a patient has disseminated lymphadenopathy, or bilateral lymphadenopathy, a diagnosis other than CSD should be sought.

Late in the course of CSD, about 10% of lymph nodes develop overlying erythema and fluctuation and may suppurate if they are not drained. Needle aspiration usually provides satisfactory drainage for suppurative CSD. If pus reaccumulates, the nodes may require open surgical drainage. The incision should be left open, with closure by granulation. Chronic fistulous tracts do not develop if CSD lymph nodes are incised and drained. This is a common misconception. In Hawaii where CSD is highly prevalent, we have followed many patients with large CSD-infected lymph nodes that progressed to suppuration, reaccumulated after needle aspiration, and required open surgical drainage. All CSD-infected lymph nodes treated with incision and drainage have healed completely without fistulae.

CSD can be diagnosed reliably with serologic testing. In a seroepidemiologic study of CSD, rigid criteria were applied for the clinical diagnosis of CSD, and all of 38 patients had positive serology (sensitivity 100%), compared to only 1 of 48 controls with no direct cat exposure in the previous 2 years who had positive serology (specificity 98%) (3). Serology was performed by the CDC. In this study, 24 of 38 patients (84%) had positive titers in their initial serum obtained 1 to 2 weeks after onset of clinical CSD; the other 6 patients (16%) developed positive titers in serum obtained 4 to 8 weeks later.

Prior to the development of a confirmatory serologic test for CSD, intradermal skin testing was used for the diagnosis of CSD. However with the development of specific laboratory tests to confirm the diagnosis, the CSD skin test is no longer recommended (which was less sensitive, less specific, poorly standardized, not readily available, not approved by regulatory authorities, and is considered by some to be unsafe).

Primary care physicians should be familiar with the atypical forms of CSD, as well as the typical form. A fairly common presentation of atypical CSD is Parinaud's oculoglandular syndrome (POGS), which consists of unilateral conjunctivitis with adjacent preauricular lymphadenopathy. The palpebral conjunctivae of the involved eye displays a characteristic granulomatous lesion that measures 2 to 3 mm to >1 cm in diameter, or there may be a scratch near the eye. Although POGS can be caused by other infections, including tuberculosis, tularemia, syphilis, and lymphogranuloma venereum, it has become well established that POGS is a common form of atypical CSD (2). Infection of the eye with B. henselae may be contracted with inoculation of the organism indirectly into the eye, rather than by direct contact through a scratch, as in typical CSD. POGS is a predictable self-limited infection with a good outcome in essentially all cases.

Hepatosplenic CSD is an atypical form of CSD which occurs in immunocompetent patients who present with fever of unknown origin (4). These patients have daily high fevers, often in the range of 40 degrees (104 degrees F), and some patients will have been febrile for a month before the diagnosis is finally made. Many of these patients complain of abdominal pain. In many cases, the care provider has neglected to ask about cat exposure until the patient has been febrile for several weeks. Physical examination is remarkably benign. Although these patients usually have a few well-healed cat scratch scars, these are often overlooked. Only about half of these patients have lymphadenopathy. They do not have hepatosplenomegaly or jaundice, and liver function tests are usually normal. The ESR may be moderately elevated, in the range of 40 to 70 mm/hr, but other screening laboratory tests are usually normal. Diagnosis is made by the presence of lytic lesions in the liver and/or spleen on ultrasound or CT scan, and B. henselae titers are positive, often markedly so. Fever usually resolves with a day or two of starting treatment with an intravenous aminoglycoside; however fever may not resolve for a month, even with adequate treatment (2).

CSD encephalopathy (CSDE) was first reported in 1952 and has recently been extensively reviewed (2). Convulsions occur in about half of cases, and may last only a few minutes or may last 3 to 4 hours, requiring intubation and intensive care. Another neurologic form of atypical CSD is a distinctive type of neuroretinitis, called Leber's stellate neuroretinitis. It presents with painless unilateral, rarely bilateral, loss of vision with central scotomata, optic disc swelling, macular star formation and complete recovery of vision within 1 to 3 months (2).

Both CSDE and CSD neuroretinitis are unusual forms of atypical CSD and are not well known to the average clinician. Immunosuppressed patients with B. henselae infection may have widespread and occasionally fatal disease (2). As these clinical syndromes become better known, along with the knowledge that laboratory tests are now available to confirm the diagnosis, these and other atypical manifestations of CSD may become more widely appreciated.

Typical CSD is a self-limited disease in immunocompetent hosts and will usually resolve spontaneously in 1 to 3 months. Recently we performed the first double-blind placebo-controlled antibiotic trial for treatment of CSD at Tripler Army Medical Center (5). Lymph node volume was measured by clinical measurement with palpation and a tape measure and by ultrasonography. This study showed that 7 of 14 (50%) azithromycin-treated patients had significant resolution of lymphadenopathy at 30 days compared to 1 of 15 (7%) of placebo-treated controls (p=0.026), as measured by ultrasonography. It should be noted that the two treatment groups had no difference in lymph node volume until the fourth week of treatment, and that clinical response at 30 days was only observed in 50% of patients in the azithromycin group. Therefore if a clinician makes a clinical diagnosis of CSD and elects to offer treatment with azithromycin (standard 5 day course), he or she should instruct the patient not to expect overnight resolution of symptoms. Azithromycin-treated patients have a 50% likelihood of having significant lymphadenopathy for 2 months or longer, despite treatment (5).

B. henselae has been reported to be sensitive to gentamicin in vitro, and anecdotal reports have supported its use in hepatosplenic disease; however the only placebo-controlled efficacy study has been with azithromycin for typical CSD lymphadenopathy.

The only way to prevent CSD is to avoid exposure to cats, particularly flea-infested cats that have had exposure to other cats, and kittens less than one year of age. There is currently no CSD vaccine for cats or humans, and antibiotic prophylaxis of humans or cats is not recommended.

Questions

1. True/False: Cat scratch disease is usually transmitted by flea-infested kittens.
2. True/False: Cat scratch disease is more common in dry, desert-like areas, as compared to humid climates.
3. True/False: Adenopathy due to cat scratch disease usually develops rapidly, within a few hours.
4. True/False: When patients have hepatosplenic cat scratch disease, their liver function tests are always abnormal, and they always have concomitant lymphadenopathy.
5. True/False: Azithromycin is the only antibiotic that has been shown to be effective in the treatment of typical CSD lymphadenopathy in a double-blind, placebo-controlled trial.
6. True/False: Serology is the diagnostic test of choice for cat scratch disease.

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Answers to questions

1. True.
2. False. Cat scratch disease is more common in humid climates because humidity is necessary for the existence of cat fleas.
3. False. Cat scratch disease adenopathy develops slowly, usually over 10-14 days.
4. False. With hepatosplenic CSD, LFTs are usually normal, and only 50% of patients have concomitant lymphadenopathy.
5. True.
6. True.

Chapter VI.30. Malaria
M. Scott Hickman, MD

This is a 10 year old male who presents to the ER with a two-month history of fever. The fever occurs every 48 hours, reaching up to 40 degrees centigrade (104 degrees F), and is often associated with a headache. Before the onset of fever, he experiences chills, nausea and vomiting. The fever resolves in two hours, followed by diaphoresis and fatigue. In between these episodes he feels well. He denies any abdominal pain, hematuria or any neurological symptoms such as a change in consciousness or seizure activity. His travel history is significant for a one month trip to Africa with his family eight months ago. His vaccinations are up-to-date, and his father states that he took prophylactic chloroquine before, during and after his trip, as well as avoiding mosquito bites at night.

Exam: VS T 38.0, P 89, RR 16, BP 100/60. Height and weight are at the 25th percentile. He is alert and active in no distress. Skin exam shows no jaundice. HEENT, neck, heart, lung and neurologic exams are normal. His abdomen exam is notable for moderate splenomegaly.

Labs: WBC 10,000, 68% segs, 20% lymphs, Hgb 10, Hct 29, platelet count 140,000, reticulocyte count 1.8%. A blood smear shows mature trophozoites and schizonts, enlarged erythrocytes and Schuffner dots, with no banana shaped gametocytes. Parasitemia is estimated at 7%.

He is hospitalized for malaria. During the night he develops a fever of 40.5 degrees. Blood cultures are negative. Anti-malarial treatment is begun with mefloquine. He responds clinically in 24 hours to treatment, with a drop in parasitemia to 5%. Primaquine is also begun for the suspected hepatic source of presumed Plasmodium vivax.

Malaria is an infectious disease caused by a protozoa (single-celled eukaryotes). It impacts an incredible toll on humanity, with an estimated 300 to 500 million world-wide cases occurring annually (1). There are an estimated 1 million deaths, most of which occur in children (2,3) between the ages of 1 and 5 years (1,4) in Africa (5). In the United States, 1000 cases of malaria are diagnosed each year with 5 to 10 deaths (6). Patients usually have traveled to endemic areas, or they are recent immigrants from these areas. In addition, physicians are often asked for advice on prophylaxis for travelers visiting malaria endemic countries.

There are four Plasmodium species of malaria in humans: P. falciparum, P. vivax, P. malariae, and P. ovale. P. vivax is the most common. P. falciparum is the most dangerous being associated with cerebral malaria. P. falciparum is different from other species in that it can cause infected red blood cells to adhere to the capillary endothelium, enabling it to evade destruction by the spleen and also causing microvascular obstructive disease.

The malaria life cycle begins when the Anopheles mosquito vector takes a blood meal (a vector transfers the infectious agent from one host to another). By doing so it releases malarial sporozoites from its salivary gland into the blood of the human host. In the pre-erythrocytic phase of the cycle, these sporozoites travel in the blood and invade hepatocytes in the liver. Here the sporozoites can take two paths. One path for sporozoites in the liver is to form trophozoites, which then undergo nuclear division to form into schizonts. Schizonts are factories of merozoites, with each schizont producing 10,000-30,000 merozoites for each infected hepatocyte. This amplifies the infectious process. The liver cells become overloaded with merozoites and burst, with merozoites spilling over into the blood stream. Merozoites then infect erythrocytes once they are released into the circulation. Hypnozoites, the other path that sporozoites can take in the liver, are found in only P. vivax and P. ovale. Hypnozoites can remain dormant in the liver for 6-11 months. When hypnozoites subsequently mature into schizonts, they produce a delayed infection and will also release merozoites into the blood to infect erythrocytes. Thus, travelers who have taken prophylactic malarial agents, as in the case above, can still become infected with malaria if the dormant liver stage is not treated for these two species. This occurs because prophylactic agents such as chloroquine or mefloquine are ineffective against the hypnozoites.

After the merozoite leaves the hepatocyte, the erythrocytic cycle begins as merozoites invade erythrocytes. The merozoite also forms into a schizont in the erythrocyte. The schizont undergoes nuclear division and merozoites are formed from this RBC schizont. The erythrocyte lyses, with merozoites released into the blood stream ready to infect other erythrocytes. The process of red blood cell invasion, merozoite formation, and erythrocyte rupture takes two to three days depending on the malarial species.

In addition, some intraerythrocytic parasites develop into sexual (gametocyte) forms, which is necessary for the completion of the sexual phase of the life cycle in the mosquito. The cycle is completed when the male and female gametocytes are taken up by the female anopheline mosquito during a blood meal from an infected individual. Fertilization takes place in the stomach of the mosquito by the formation of a zygote. This zygote divides until a oocyst develops, which eventually ruptures and releases sporozoites which find their way to the salivary glands of the mosquito. Here the sporozoites remain, ready to reinfect another human and begin the cycle once again.

P. falciparum is the most severe infection of the different plasmodium species, and it produces a microvascular disease, unlike the other species which do not. Erythrocytes infected with P. falciparum adhere to the endothelial lining of small blood vessels, causing blockage and a decrease in tissue perfusion with a resulting metabolic acidosis. Lysis of erythrocytes and the release of merozoites causes an immune response with the production of cytokines (TNF-alpha), giving rise to the characteristic fever of malaria. The anemia is caused by the lysis of red blood cells as well as by the suppressive effect that TNF- alpha has on erythropoiesis. Hypoglycemia is often seen in patients with P. falciparum. This is caused by the depletion of liver glycogen from decreased intake, glucose consumption by the parasites, and increased levels of TNF- alpha. The main organs involved include the brain, kidneys, liver, spleen, lung and GI tract, although any organ can be affected. The brain in cerebral malaria is edematous and hyperemic, with small blood vessels filled with parasitized erythrocytes (7), giving rise to the impaired consciousness and seizures of cerebral malaria. Renal failure secondary to tubular necrosis is due to increased circulating free hemoglobin (hemoglobinuria), as well as due to hypovolemia and microvascular disease. Excess hemoglobin that is spilled into the urine gives malaria one of its names: blackwater fever. The spleen, which is responsible for filtering out the deformed erythrocytes, is enlarged, congested, and at times may rupture. The liver also enlarges, as it too has reticuloendothelial function. Parasitized RBCs sequestered in the pulmonary vasculature can cause cough, respiratory distress and pulmonary edema. In the gastrointestinal tract, it can cause gastroenteritis.

Infected erythrocytes in the placenta can cause increased mortality, premature delivery and low birth weight. Congenital infections in newborns are also seen if erythrocytes cross the placenta. Anemia in the mother is further worsened by malaria. P. vivax, P. ovale and P. malariae do not cause a microvascular disease because they do not cause erythrocytes to adhere to vascular endothelial cells. They do cause hemolysis and an inflammatory response, giving rise to a less severe form of the disease than that seen with P. falciparum. Sickle-cell anemia, beta-thalassemia and glucose-6-dehydrogenase deficiency are thought to offer resistance to malaria in the heterozygote forms. This protection is believed to come from the shortened RBC life-span with increased RBC susceptibility to lysis from oxidative stress (interrupting the Plasmodium reproductive cycle) and the fact that the hemoglobin with these genetic variants denatures preferentially with malaria infection, releasing toxic forms of heme that damage the parasites. In addition, P. vivax requires the Duffy blood group antigen to bind to the RBC and cause an infection. West Africans and many Americans of African descent are often missing this blood group antigen, rendering them resistant to this species. Acquired resistance comes about with IgG and IgM, with IgG giving protection against merozoites, preventing them from invading susceptible erythrocytes. This immune response renders individuals resistant to symptomatic disease. They are not however immune, as their body still can harbor parasites even though they are non-symptomatic.

The clinical manifestations of fever coincide with the rupture of the red blood cells and the release of merozoites, stimulating the production of TNF-alpha. Different malarial species have different patterns of growth, with erythrocytic schizogony and the release of a brood of merozoites occurring approximately every 48 hours (called tertian malaria) for P. falciparum, P. vivax, and P. ovale, and 72 hours (called quartan malaria) for P. malariae. If there is more than one brood of parasites developing in the blood at one time, then the fever can occur daily, obscuring the diagnosis. P. falciparum in particular is known for causing any pattern of fever. The pre-erythrocytic phase is asymptomatic, as sporozoites are released from the mosquito and pass to the hepatocytes.

An attack classically starts with the "cold stage", with chills lasting from minutes to an hour. Nausea, vomiting and frequent micturition are often seen during this phase. Following the cold stage, the "hot stage" begins with fevers between 40 (104 F) to 41 (106 F) degrees C lasting between 2 to 6 hours, associated with a severe headache, tachycardia, delirium, epigastric pain, nausea, vomiting and diarrhea. Despite the high fever, there is minimal diaphoresis. After the hot stage, the third "sweating phase" is entered lasting 2 to 3 hours, with diaphoresis, resolution of the fever, and fatigue that gives way to sleep. In children less than 5 years of age, the signs may be non-specific: fever, vomiting, abdominal pain and diarrhea. Older children may only complain of fever, headache and joint pain. For these reasons, fever in a child that has visited or lives in a malaria endemic area is considered to be due to malaria until proven otherwise.

The clinical manifestations of cerebral malaria include altered consciousness, seizures, symptoms of raised intracranial pressure, opisthotonos, decorticate or decerebrate posturing, hypotonia and conjugate eye movements. It has a high case fatality rate (8). On physical exam, signs of anemia should be sought. Respiratory distress and splenomegaly may be present. Dehydration due to decreased PO intake and increased losses from diaphoresis or diarrhea can give rise to hypotension, tachycardia and shock.

Besides having 4 different species of malaria, there are also many strains of malaria, (except for P. malariae which has only one). This diversity makes vaccine development for malaria very difficult. As stated above, in areas where malaria is endemic, repeated infections cause the development of acquired immunity from symptomatic disease (they are still susceptible to asymptomatic parasitemia). For this reason, most cases of fatal malaria occur in the first 5 years of age in these areas. In contrast, in areas with no endemic infection (such as the United States), acquired immunity is not developed and fatal malaria can occur at any age.

Laboratory findings include a decreased hemoglobin, hematocrit, thrombocytopenia and increased bilirubin due to the lysis of red blood cells. Hyponatremia, hypokalemia, and hypercalcemia may be seen. Acute renal failure with increased creatinine, proteinuria and hemoglobinuria may be present. Diagnosis is made by examination of the thick and thin smears. Thick smears allow the detection of the parasite in small numbers, while the thin smear allows one to identify the species. Classically the ring form of P. falciparum is seen. Microscopic examination can give a quantitative value to the parasitemia, with more than 5% to 10% of erythrocytes being infected associated with high mortality rate. Following the percentage of infected erythrocytes serially, is useful to evaluate treatment. PCR and ELISA can also be used in the diagnosis.

P. falciparum differs from P. vivax and P. ovale in several ways (9):

	P.falciparum	P.vivax/P.ovale
Multiple infected erythrocytes:	common	rare
Mature trophozoites or schizonts:	absent	common
Schüffner dots:	absent	common
Enlarged erythrocytes:	absent	common
Banana-shaped gametocytes:	common	absent

The correct diagnosis of P. falciparum is important. Looking at the table above, you would expect the more severe infection of P. falciparum to have multiple infected erythrocytes, with the more mild infection of P. vivax and P. ovale to have rare infected erythrocytes. Mature trophozoites and schizonts are not seen with P. falciparum because they are sequestered in the peripheral microvasculature. P. vivax preferentially infects a reticulocyte, so infections with P. vivax show large erythrocytes. Schüffner dots are due to pigment accumulation in infected erythrocytes, and appear blue on microscopic examination. They are characteristic of P. vivax and P. ovale infections. P. falciparum can be distinguished by its early trophozoites called ring forms (signet-ring appearance), and by the sausage or banana shape of its gametocytes.

The differential diagnosis of malaria is broad, including leptospirosis, yellow fever, juvenile rheumatoid arthritis, Hodgkin's disease, brucellosis, borreliosis, pneumonia, meningitis, tuberculosis, influenza and bacteremia (9).

Uncomplicated malaria is defined as a child with fever and a positive blood smear, but without evidence of altered consciousness, hypoglycemia, respiratory problems, jaundice or severe anemia. Severe malaria includes the fever and positive blood smear as above, but also involves mental status changes, convulsions, hypoglycemia, acidosis, jaundice, weakness or parasitemia greater than 15%. Uncomplicated malaria can be managed on an outpatient basis for a child who has lived in an endemic area all of their life. The management of an infected patient who has visited an endemic area for the first time, or a patient with severe malaria, involves hospital admission. Patients suspected of having P. falciparum should always be hospitalized, with early initiation of therapy. Conventional treatment of dehydration, hypoglycemia, anemia, seizures, pulmonary edema and renal failure is required. The selection of an antimalarial depends on the species identified or suspected, the possibility of resistance, and the ability of the patient to take oral medications. Chloroquine is the drug of choice for plasmodia sensitive to this drug. For chloroquine-resistant P. falciparum, oral therapy includes quinine with pyrimethamine-sulfadoxine, tetracycline, doxycycline or clindamycin. Mefloquine is another alternative. Chloroquine-resistant P. vivax should be treated with mefloquine. Primaquine is effective against the liver forms of P. vivax and P. ovale. A new anti-malarial drug with fewer side effects than mefloquine is atovaquone/proguanil (Malarone). Exchange transfusion can be considered in patients with severe disease. Most patients treated with chloroquine respond within 24 hours, and usually recover by the third or fourth day (12). The case fatality rate for cerebral malaria even with optimal therapy, is 15-30%, with 10% of survivors of cerebral malaria having residual signs of ataxia, hemiparesis and spasticity.

Prevention involves an assessment of the risk of the country one is visiting, along with chemoprophylaxis and methods to limit mosquito bites by Anopheles (which feed primarily from dusk to dawn). Permethrin-impregnated mosquito nets, long-sleeve shirts, and 35% DEET repellant sprays, limit exposure to Anopheles. Chloroquine can be taken on a weekly basis for chemoprophylaxis. It is taken 2 weeks before departure (to monitor for side effects), continued for the duration of the trip, and 4 weeks after leaving the endemic area. It is the drug of choice for chemoprophylaxis because it is safe for all ages and during pregnancy. Mefloquine (taken once weekly) is used for areas suspected of having chloroquine-resistant P. falciparum (Southeast Asia, the Amazon region of South America, and sub-Saharan Africa). In patients weighing less than 15 kg or for pregnant women, chloroquine combined with proguanil can be used. Doxycycline is an alternative for those older than 8 years (10,11). A newer alternative is atovaquone/proguanil, but this must be taken daily.

Questions

1. The species of malaria associated with adherence to endothelial walls, cerebral malaria, and a high mortality rate is:
    a. P. falciparum
    b. P. vivax
    c. P. malariae
    d. P. ovale

2. The fever of malaria:
    a. can be tertian (occurring every 48 hours).
    b. can be quartan (occurring every 72 hours).
    c. occur with no pattern at all.
    d. all of the above.

3. The clinical manifestations of the cyclic fever of malaria are caused by the:
    a. pre-erythrocytic phase
    b. hepatic stage
    c. erythrocytic stage
    d. sexual stage

4. Liver hypnozoites (dormant form) can be effectively treated with:
    a. chloroquine
    b. mefloquine
    c. primaquine
    d. doxycycline

5. The pathogenesis of malaria can affect which of the following organ systems:
    a. liver
    b. brain
    c. lungs
    d. kidneys
    e. spleen
    f. GI tract
    g. all of the above

6. Prophylaxis for malaria includes all of the following except:
   a. chloroquine
   b. mefloquine
   c. permethrin impregnated mosquito nets
   d. 35% DEET
   e. avoiding mosquitoes during the day

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Answers to questions

1. a. P. falciparum is unique among malarial species in that it has mechanisms to adhere to vascular endothelial walls. This produces a microvascular disease, leading to poor perfusion and metabolic acidosis. This hypoperfusion can affect almost any organ in the body, but this is of greatest significance in that it can cause cerebral malaria, which can cause a change in consciousness and seizures. Long-term affects due to cerebral malaria can also be seen. P. vivax is the most common form of malaria, but produces a more milder form of the disease.

2. d. The fever of malaria can produce any pattern of fever, with P. falciparum most known for its lack of recognizable fever patterns. Classically, the release of merozoites from red blood cells all in one group at similar times causes an inflammatory response, the production of TNF-alpha, and a characteristic pattern of fever depending on the particular species. The fever occurs approximately every 48 hours (called tertian malaria) for P. falciparum, P. vivax, and P. ovale, and 72 hours (called quartan malaria) for P. malariae.

3. c. The life cycle of malaria is very complex. It starts with malarial sporozoites being released from the anopheles mosquito. In the pre-erythrocytic stage sporozoites travel to the liver, with the patient being asymptomatic during this time. Sporozoites form schizonts, which eventually produce thousands of merozoites. These merozoites are released from hepatocytes, and infect red blood cells, giving rise to the erythrocytic stage of the life cycle. The erythrocytes burst after infection, releasing merozoites, which is the major cause of the cyclical fever. These merozoites can infect new blood cells, or form gametocytes. Male and female gametocytes are taken up by the mosquito, where they reproduce and form new sporozoites, completing the life-cycle during the mosquito's next blood meal.

4. c. Sporozoites infecting the liver can form into schizonts and can also form hypnozoites. These can remain dormant in the liver, causing an infection months later. The dormant liver-stage of the malarial life cycle, seen in P. vivax and P. ovale, is effectively treated with primaquine.

5. g. The microvascular disease of P. falciparum can affect almost any tissue of the body, giving rise to the many clinical features of malaria.

6. e. Prophylaxis for malaria includes using permethrin impregnated mosquito nets, avoiding mosquito bites using 35% DEET, and chemoprophylaxis most commonly with chloroquine or mefloquine. The anopheles mosquito usually bites from dusk to dawn, not during the day, and it is during these times that travelers should be particularly careful.

Chapter VI.31. Protozoans and Parasites
Loren G. Yamamoto, MD, MPH, MBA

A 2 year old boy from in a war refugee camp is treated for dehydration secondary to vomiting and foul diarrhea. After rehydration, the staff suspects that he may have Hirschsprung's disease based on his history and growth pattern. He is flown to your hospital for surgical evaluation. He is obviously malnourished and underweight, but he improves clinically. After eating lunch, the boy vomits and the nurses note the presence of several large worms in the vomitus. They later note that he has a visible worm in his stool. A stool sample is sent for ova and parasite analysis which identifies Giardia cysts and ascaris eggs. He is treated with albendazole which covers both the Giardia and ascaris.

Protozoans and parasites are less common in the United States. Many of them require fecal-oral transmission or vectors (insects and rodents). Proper public health measures which are taken for granted in the U.S. are responsible for minimizing our exposure to these infections. These measures include regulations and laws ensuring clean water, agriculture and livestock, proper food handling, sanitation (sewage and trash disposal), vector control (insects and rodents), and housing. American lifestyle factors including good nutrition, footwear and skin care also reduce the risk of infection.

Protozoans are eukaryotic large single celled organisms. Parasites are organisms which live in or on another organism, which would include viral and bacterial infections as well. However, the general understanding when one refers to parasites, is that these include "worms" such as roundworms and flatworms. Since many of these organisms are gastrointestinal, common presentation patterns include gastroenteritis, failure to thrive, weight loss, edema, and or abdominal discomfort. The immune system has a difficult time eradicating protozoans and parasites. Eosinophilia is often associated with parasites, but eosinophilia is only present in the presence of invasive worms.

Protozoans can be classified into ameba, flagellates and sporozoans. Pneumocystis used to be considered a protozoan, but it now classified as an opportunistic fungi.

Ameba include Entamoeba histolytica often called amebiasis, which classically causes bloody diarrhea (amebic dysentery), but it may also present with non-specific gastroenteritis, edema, failure to thrive or an amebic liver abscess. The diagnosis can be made by finding organisms in the stool or by serology. Naegleria fowleri is a rare and fatal infection. Naegleria live in hot springs, so most infections are acquired by swimming or diving in hot springs. Naegleria enter the body and infect the brain rapidly resulting in encephalitis, coma and death (often despite treatment).

Flagellates include giardia, trichomonas, trypanosomes and leishmania. Giardia lamblia causes diarrhea, malabsorption and abdominal discomfort. Giardia organisms are generally not found in stool samples, and Giardia cysts are only sometimes found in the stools. Giardia organisms were most commonly identified by having the patient swallow a gelatin capsule on a string which is then retrieved and analyzed. Giardia serology has now replaced these other methods of identifying giardiasis.

Trichomonas vaginalis (trich for short) is a sexually transmitted motile protozoan which causes vaginitis. Clinically, a pruritic vaginal discharge results, with or without dysuria. Motile protozoans are seen on a microscopy wet mount of the vaginal discharge. Males are often asymptomatic.

Trypanosomiasis can be of the African or the South American type. African sleeping sickness is caused by Tryp. brucei rhodesiense and Tryp. brucei gambiense, which are both spread by the biting tsetse fly vector. Symptoms of infection include fever, headache, malaise, rash, lymphadenopathy, etc. Spontaneous remission or coma and death may follow. American trypanosomiasis (also known as Chagas disease) is cause by Tryp. cruzi which is spread by the reduviid bug. Cardiomyopathy may classically result, but other presentations include malaise, fever, lymphadenopathy, encephalitis and death.

Leishmania infections are transmitted by sandfly vectors. Leishmania donovani causes visceral leishmaniasis (also known as kala-azar) which results in fever, malaise, lymphadenopathy, organomegaly, anemia and weight loss. Leishmania tropica cause cutaneous leishmaniasis. Leishmania braziliensis causes mucocutaneous leishmaniasis.

Sporozoans include cryptosporidium, plasmodium and toxoplasma. Cryptosporidium may be a contaminant in some water systems. It is resistant to chlorination, but many home filtration systems will filter out the cysts. Infection with cryptosporidium results in self limited diarrhea in healthy persons (no treatment required), but in immunocompromised individuals, it may cause fever, chronic diarrhea, weight loss, and death.

Malaria is caused by the various Plasmodium species (ovale, vivax, falciparum, malariae). Malaria is a complex infection which is described in a separate chapter. It is transmitted by anopheles mosquito vectors and it can be prophylaxed and treated to a limited extent with chloroquine and primaquine.

Toxoplasma gondii is harbored by cats. Infection can be acquired by exposure to cat feces (by touch or through contaminated food). Most healthy adults have an asymptomatic or a non-specific illness similar to infectious mononucleosis. Infection in pregnant mothers during early gestation puts the fetus at risk of congenital toxoplasmosis which may result in brain injury, microcephaly and chorioretinitis. Immunocompromised patients may develop chorioretinitis and focal brain lesions.

Trematodes (also called flukes) are unsegmented flatworms which contain the groups fasciola, clonorchis, paragonimus, and schistosoma. Intestinal flukes include fasciolopsis buski found in Asia. Clonorchis sinensis (the Asian liver fluke) is acquired by eating raw or undercooked freshwater fish. Fasciola hepatica (another liver fluke) is found in sheep raising areas and infection is acquired by eating organisms which have contaminated agriculture. Paragonimus westermani is a lung fluke found in Asia and Africa. It is acquired by eating contaminated shellfish. Schistosomes are classified as blood flukes because they spread through the circulation. Schistosoma species include mansoni, japonicum, and haematobium. These organisms can penetrate the skin directly when exposed to contaminated water. S. mansoni and S. japonicum cause intestinal symptoms. S. haematobium causes bladder symptoms including bladder carcinoma.

Cestodes (also called tapeworms) are segmented flatworms. Taenia solium is the pork tapeworm and Taenia saginata is the beef tapeworm. Humans acquire these when ingesting undercooked pork and beef that are contaminated with larval forms known as cysticerci. In most instances, intestinal infection with large tapeworms result. In some instances, cysticerci invade the eye or brain resulting in focal brain lesions which often leads to seizures known as neurocysticercosis. This is very common in countries where livestock raising conditions are not well regulated and undercooked pork is frequently consumed. The southern U.S. regions encounter frequent cases of neurocysticercosis in Mexican immigrants and visitors. The fish tapeworm, Diphyllobothrium latum, is found in undercooked freshwater fish. This organism has largely been eliminated from previously endemic areas in Minnesota (the land of lakes) and the Great Lakes. Raw

salmon ingestions may be a source of D. latum, because even though salmon are salt water fish, they may acquire the infection when they return to freshwater.

Nematodes are roundworm groups which can be remembered by the mnemonic NEMATODES (with 2 As and 3 Ts). These stand for Necator, Enterobius, Mosquito borne (Wucheria and Brugia), Ascaris, Ancylostoma, Trichuris, Trichinella, Toxocara, Onchocerca, Dracunculus, Eye worm (Loa loa), and Strongyloides. They infect humans via ingestion (EATT: Enterobius, Ascaris, Trichuris, Trichinella) or by skin penetration (SAN: Strongyloides, Ancylostoma, Necator).

Necator americanus and Ancylostoma duodenale are hookworms which are endemic in warm moist climates. N. americanus is endemic in the southeast U.S. Larvae in the soil attach (hook) between the toes and penetrate the skin into the bloodstream. They migrate into the lungs causing an eosinophilic pneumonia. Organisms are coughed up and swallowed where they enter the GI tract. They attach (hook) to the intestinal wall where they cause a chronic infection.

Enterobius vermicularis (pinworms) are the most common parasite in the U.S. Many children are said to have these and they are usually asymptomatic. It is likely that spread occurs among young children with poor oral hygiene habits in group settings (e.g., preschool). These worms are about 0.7 cm long and they resemble moving pieces of white thread. They are usually found in the perianal area. These worms reside in the rectum. They exit the anus and lay eggs at night when the child is asleep. The worms then reenter the anus. Some advocate obtaining a perianal sample by applying sticky tape or an adhesive plastic paddle to the anus several hours after the child has fallen asleep. Alternatively, visual inspection at night will often identify the worms. In girls, the worms may enter the vagina instead of the anus. This will cause dysuria or vaginal pruritus. This is commonly seen in emergency departments at night. If the parent brings the child in early, the moving worms are usually still visible in the perineal area. If the parent brings the child in late, dead degenerating worms may be visible in the perineum. Otherwise, a chief complaint of sudden onset of dysuria or vaginal discomfort in the absence of urinalysis evidence of a UTI, is suggestive of pinworms. These can be eradicated with a single dose of mebendazole. This can be repeated in two weeks to reduce the likelihood of reinfection.

Ascaris lumbricoides is probably the most common parasitic worm in the world. If you see a large intestinal worm, odds are this is what it is. They are large and pink resembling smooth earthworms. Ascaris worms survive and grow in the intestine. Infection may be asymptomatic or they may grow large enough to cause a bowel obstruction. Newly hatched larvae may migrate throughout the body into the liver, heart and lungs. Eosinophilic pneumonia is caused by migrating ascaris larvae as they invade the lungs.

Mosquito borne nematodes include Wucheria bancrofti and Brugia malayi which both cause elephantiasis. These are difficult to treat. These infestations are referred to as filariasis, which also includes Loa loa (an African eye worm, which is spread by the Chrysops fly vector) and Onchocercal volvulus (also known as river blindness, which is spread by the Simulium blackfly).

Trichuris trichiura (whipworm) is found in tropical regions. The infestation can be asymptomatic or the usual GI chronic infestation symptoms. Trichinella spiralis is the pork roundworm, which is acquired by eating poorly cooked contaminated pork. The larvae initially cause GI infestation symptoms. As maturing worms lay new eggs, these larvae hatch and migrate into the bloodstream where they lodge in muscle tissue forming calcifications which cause fever and myalgia. Toxocara canis and Toxocara cati are dog and cat parasites which may be asymptomatic or cause visceral larvae migrans.

Dracunculus medinensis is known as the Guinea worm. Larvae in tiny aquatic crustaceans are ingested in contaminated water. Over time, adult worms grow subcutaneously (nearly one meter long), which are classically removed through the skin by gradually pulling them (rolling them onto a stick).

Strongyloides stercoralis (threadworm) is another parasite that enters the body through exposed feet stepping over contaminated soil.

Commonly used antiparasitic drugs include albendazole, pyrantel pamoate, mebendazole and metronidazole. It should be noted that this chapter is written for general background information only. Therapeutic decisions should be based on more comprehensive information describing each infection type. Some parasitic infections do not benefit from treatment.

Albendazole is a relatively new drug which covers a broad range of parasitic infections. Mebendazole (Vermox) and pyrantel pamoate are older drugs which are also highly efficacious. Metronidazole (Flagyl) and tinidazole have activity against many protozoans. Many parasites respond to albendazole and pyrantel pamoate. Diethylcarbamazine is used for filariasis parasites (and dog heartworms). Praziquantel works for most flatworms (flukes and tapeworms).

Summary of Protozoans and Parasites (Treatment agents in parentheses. Alb=albendazole, Pyr=pyrantel pamoate, Meb=mebendazole, Metr=metronidazole) [Route of infection in brackets]. [FO] = fecal-oral transmission. The purpose of this summary is to provide a general educational overview. Note that treatment alternatives, doses and durations are not provided here. Please use a current authoritative reference for clinical therapeutic decisions.

I. Protozoans
- A. Ameba
  1. Entamoeba histolytica (Metr) [FO]
  2. Naegleria fowleri (amphotericin) [hot springs]
- B. Flagellates
  1. Giardia lamblia (Metr) [FO, contaminated water]
  2. Trichomonas vaginalis (Metr) [sexually transmitted]
  3. Trypanosomes
     a. Tryp cruzi (nifurtimox or benznidazole) [reduviid bug vector]
     b. T. rhodesiense, T. gambiense (pentamidine) [tsetse fly vector]
  4. Leishmania (stibogluconate) [sandfly vector]
- C. Sporozoans
  1. Cryptosporidium (paromomycin, amphotericin) [drinking water]
  2. Plasmodium-Malaria (complex treatment) [anopheles mosquito vector]
  3. Toxoplasma (pyrimethamine) [cat feces, contaminated food]

II. Trematodes (flukes)
- A. Intestinal: Fasciolopsis buski (praziquantel) [FO]
- B. Liver
  1. Clonorchis sinensis (praziquantel) [raw freshwater fish],
  2. Fasciola hepatic (triclabendazole) [sheep-raising area, contaminated agriculture]
- C. Lung: Paragonimus westermani (praziquantel) [shellfish]
- D. Blood: Schistosoma (praziquantel) [skin penetration in contaminated water]

III. Cestodes (tapeworms)
- A. Beef: Taenia saginata (praziquantel, albendazole) [ingesting contaminated raw beef]
- B. Pork: Taenia solium (praziquantel, albendazole) [ingesting contaminated raw pork]
- C. Fish: Diphyllobothrium latum (praziquantel) [ingesting infected raw freshwater fish]

IV. Nematodes (roundworms): NEMA(2)T(3)ODES
- A. Necator (albendazole) [FO, skin]
- B. Enterobius (mebendazole) [FO]
- C. Mosquito borne
  1. Wucheria bancrofti (diethylcarbamazine) [mosquito vector]
  2. Brugia malayi (diethylcarbamazine) [mosquito vector]
- D. Ascaris (pyrantel pamoate, albendazole) [FO]
- E. Ancylostoma (albendazole) [FO, skin]
- F. Trichuris (mebendazole) [FO]
- G. Trichinella (mebendazole) [poorly cooked pork]
- H. Toxocara (albendazole) [dog and cat feces]
- I. Onchocerca: river blindness (ivermectin) [Simulium blackfly vector]
- J. Dracunculus: Guinea worm (metronidazole) [contaminated water]
- K. Eye worm: Loa loa (diethylcarbamazine) [Chrysops fly]
- L. Strongyloides: threadworm (ivermectin) [FO, skin]

Questions
1. Name two parasites which are associated with the ingestion of uncooked freshwater fish?
2. What is the most common parasitic worm in American children?
3. Name two parasites associated with the ingestion of poorly cooked pork?
4. Name two motile (flagellated) protozoans infections commonly found in the U.S.
5. Name two types of hookworms.
6. Name four protozoans and two parasites transmitted by mosquito vectors.
7. Name 3 or 4 protozoans and parasites that are transmitted by biting flies.
8. Name 2 or 3 protozoans and parasites that invade the brain.

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Answers to questions
1. Diphyllobothrium latum (fish tapeworm), Clonorchis sinensis (Asian liver fluke),
2. Pinworms (Enterobius vermicularis).
3. Trichinella spiralis, Taenia solium.
4. Trichomonas vaginalis, Giardia lamblia.
5. Ancylostoma duodenale, Necator americanus
6. Malaria (Plasmodium vivax, falciparum, haematobium, malariae), filariasis (Wucheria bancrofti, Brugia malayi).
7. Tryp cruzi [reduviid bug vector, which is not really a fly, but it is a biting bug], T. rhodesiense and T. gambiense [tsetse fly vector], leishmania [sandfly vector], Onchocerca [Simulium blackfly vector], loa loa eye worm [Chrysops fly].
8. Taenia solium (neurocysticercosis), Naegleria fowleri, Toxoplasmosis, Loa loa (eye).

Chapter VI.32. Candida and Fungal Infections
Wendy C. Matsuno, MD

This is a 14 year old male who presents to the office with tender, itchy feet. He has been having persistent itchiness of his toes, particularly between the fourth and fifth toes for the last week. He has been otherwise healthy, and even boasts that he is playing for the community football team.

Exam: VS T 37.0, P 74, R 12, BP 118/64. Ht/Wt at the 50th percentile. The patient is alert, active and in no distress. His physical exam is unremarkable except for his feet. The toes on both feet are inflamed and some scaling of the skin is noted. The interdigital space, between the fourth and fifth toes, appears to be the most affected. There is some cracking and thickening of the anterior plantar surfaces.

A culture of the area is taken and he is prescribed topical tolnaftate cream. He is also advised to use slippers when in the locker room showers, and to wash his feet well when he bathes at home. A week later, he returns with some relief of his symptoms. The results of the culture identify Trichophyton rubrum and Candida albicans. His topical therapy is changed to clotrimazole cream (an imidazole) applied twice daily for 3-4 weeks, since tolnaftate does not cover Candida albicans.

Superficial fungal infections of the skin, nails and hair are common (1). The fungi causing these infections are one of three types: dermatophytes, Candida species or Malassezia furfur. The recent increased incidence has been attributed to a greater number of immunocompromised hosts, use of chemotherapeutic agents, lifestyle changes (increased use of health clubs) and the large elderly population (1). Superficial infections can progress to systemic infections, but systemic and disseminated fungal infections are serious infectious which require inpatient care by infectious disease specialists, that are beyond the scope of this chapter.

Dermatophytoses is a common fungal infection caused by three genera of filamentous fungi: Trichophyton, Microsporum, and Epidermophyton. These organisms can infect any keratinized epithelium, nail and hair follicle because they utilize keratin as a nutrient. Trichophyton species infect skin, nails and hair, with T. rubrum the most common organism (2). Microsporum species primarily invade the hair, while Epidermophyton species invade the intertriginous skin.

Dermatophytoses are classified by the natural habitat in which they grow. Anthropophilic dermatophytes are those acquired from humans and can cause chronic low-grade infections to acute inflammatory disease. Geophilic dermatophytes infect humans sporadically causing an inflammatory reaction and are acquired from the soil. Zoophilic dermatophytes are acquired from animals through direct or indirect contact. The name of the infection itself is determined by the word 'tinea' followed the Latin word for the site of involvement.

Tinea capitis is a dermatophyte infection of the scalp (3). Prior to the 1900s, the most common cause of tinea capitis was Microsporum canis (4). In 1900-1940, M. audouinii was found to be the prominent cause of tinea capitis in North America and Western Europe (4). Since 1952, however, the incidence of tinea capitis caused by T. tonsurans has steadily risen and is now the primary cause of tinea capitis in the United States (4).

The presentation of tinea capitis caused by T. tonsurans can be of either the inflammatory or non-inflammatory type. The inflammatory type occurs in about 40% of cases, and can be accompanied with a kerion (edematous boggy nodule) or dermatophytid "id" reaction (fungus-free, papular eruption, usually on the trunk) (5). The non-inflammatory type occurs in the remaining 60% of cases (5). It presents with scaling in a dandruff-like manner or in a "black-dot" pattern with well demarcated areas of hair broken off at the orifice leaving the appearance of black dots. Posterior occipital and cervical adenopathy may be present.

The differential diagnosis of tinea capitis includes seborrheic dermatitis, psoriasis, alopecia areata, trichotillomania and some dystrophic hair disorders. With the presence of a kerion, a bacterial infection must be considered. In high risk individuals, the presence of patchy, moth-eaten alopecia could be a sign of secondary syphilis. Also, in cases with chronic tinea capitis, the diagnosis of discoid lupus and lichen planopilaris is also possible.

The diagnosis of tinea capitis must be done by potassium hydroxide (KOH) preparation or culture. Wood's light examination is not used because T. tonsurans, the most common causal organism in the US, does not fluoresce. In doing a KOH mount, "black dots" or scrapings from scaly areas should be collected, mixed with 10-20% KOH solution, heated and examined under the microscope. A KOH mount may give a false negative in the case of early or inflammatory lesions. Thus, a culture should be done. The most popular method to collect the culture is by the brush technique where a toothbrush is run over the scalp to pick up scales and hair debris. The culture is then plated on Sabouraud's dextrose agar with cycloheximide and chloramphenicol or on dermatophyte test medium. The culture will usually show growth in 7-10 days.

Topical therapy alone is ineffective in the treatment of tinea capitis (3). Topical therapy with 2.5% zinc sulfide or zinc pyrithione shampoo is helpful in decreasing the shedding of spores, but oral therapy is also needed to eradicate the infection. Oral therapy is often done with griseofulvin, which is currently the only drug approved by the U.S. Food and Drug Administration for the treatment of tinea capitis in children (4). In 1997, the recommended dose and duration of treatment with griseofulvin by the Infectious Disease Committee of the American Academy of Pediatrics was 10-20 mg/kg/d (using the microsize formulation of griseofulvin) for 4 to 6 weeks, with the intention of treatment continuing until 2 weeks after clinically asymptomatic (4). If the ultramicrosize formulation of griseofulvin is used, 5-10 mg/kg/day in a single or two divided doses is the recommended dosage (not to be used in children under 2 years of age). However, most experts use a dose of 20 mg/kg/d (microsize). "Microsize" refers to the product formulation of griseofulvin. The other preparation is ultramicrosize. The difference is that microsize has an absorption of 25-75% after an oral dose vs ultramicrosize which is almost completely absorbed. So an oral concentration of 500 mg of microsize griseofulvin produces similar serum concentrations to 250-330mg of ultramicrosize griseofulvin. The Microsporum species that were the primary causes of tinea capitis in past years, are more sensitive to griseofulvin than T. tonsurans, which explains why tinea capitis is currently more difficult to treat.

Three other agents are also being investigated: terbinafine, itraconazole, and fluconazole. Terbinafine at a dose of 5-11 mg/kg (depending on level of involvement) was used for 1, 2 and 4 weeks with an overall cure rate of 44%, 57%, and 78% respectively (1). In a comparison of terbinafine with griseofulvin, the primary response rates in 50 patients treated for 8 weeks were found to be 72% and 76%, respectively (4). However, at 12 weeks, fewer recurrences were seen with terbinafine with an efficacy of 76% as compared to griseofulvin with an efficacy of 64% (4). In cases of tinea capitis caused by Microsporum species, terbinafine was found to be less effective than griseofulvin with only a 32% cure rate 14 weeks after a 6-week course of therapy (4). Disadvantages of terbinafine include its decreased effectiveness against Microsporum species (compared with griseofulvin), gastrointestinal disturbances seen in 5% of patients and the potential for interactions with other drugs, such as rifampin and cimetidine (4).

Studies are also being conducted with itraconazole and fluconazole. The dosing for itraconazole is 5 mg/kg or 100 mg/day for 2-6 weeks (4). A 6-week course of itraconazole was found to be comparable to a 6-week course of griseofulvin (4). For fluconazole, a study

of 44 children infected with T. tonsurans, demonstrated that a dose of 6 mg/kg for 20 days was found to be safe with an efficacy of 89% (1). Itraconazole and fluconazole were found to cause minor gastrointestinal side effects in 5% of patients and cause a reversible, asymptomatic elevation in liver function tests in 1 of 17 patients (4).

Tinea pedis, more commonly known as athlete's foot, is the most common fungal infection (1). The usual etiologic agents are T. rubrum (most common), T. mentagrophytes and E. floccosum (1). Non-dermatophytes and candida species can coexist or produce similar infections. Predisposing factors include occlusive footwear, hot, humid weather, and walking barefoot on contaminated floors. Arthrospores are able to survive for 12 months in flakes of human skin cells.

Tinea pedis is usually seen in preadolescent and adolescent males, and less likely in younger children (3). The toe webs and soles of the feet, most commonly the lateral toe webs, are usually affected. Patients often present with severe tenderness, pruritus, foul odor, fissuring, scaling and maceration of the surrounding skin. In some cases, a diffuse hyperkeratosis of the sole of the foot with mild erythema is seen. In infections with T. mentagrophytes, usually in young children, an inflammatory vesicular reaction is seen on the dorsal surface of the foot. Breaks of the skin may occur leaving a pathway for bacterial infection with group A streptococcus or Staphylococcus aureus. The infection may also spread to the inguinal area (tinea cruris), trunk (tinea corporis), hands (tinea manuum), or nails (tinea unguium).

The differential diagnosis includes normal peeling of the interdigital spaces and infection by Candida or other bacterial organism. Contact dermatitis, atopic dermatitis, and dyshidrotic eczema can also mimic tinea pedis (3).

The diagnosis of tinea pedis can be made by KOH slide examination or by culture. On KOH microscopic examination, fungal mycelia or hyphae are seen. Fungal culture can also reveal the diagnosis. The use of a Wood's lamp can demonstrate erythrasma (coral red fluorescence under the Wood's lamp), but does not provide definitive diagnosis of tinea pedis.

The treatment of tinea pedis involves topical and systemic agents to cure and to prevent recurrence. Topical therapy with tolnaftate, imidazoles (e.g., miconazole or clotrimazole), ciclopirox, etc., can be used once or twice daily for 1-4 weeks (1). Tolnaftate, however, can only be used in uncomplicated cases, since it is not effective against Candida species (3).
Systemic therapy with an imidazole (e.g., oral ketoconazole, itraconazole) is usually sufficient. In one study of 484 patients enrolled in 15 different studies, itraconazole, 200mg twice a day for one week, was found to be highly effective with a cure rate of 85% (1). Thus, this is the recommended regimen for plantar type tinea pedis.

Secondary prophylaxis of tinea pedis is important because recurrences are common. Preventive measures include avoidance of occlusive footwear, use of footwear when bathing in public showers, and complete drying of the area between the toes after bathing. The use of absorbent anti-fungal powder, such as zinc undecylenate (Desenex), which does not cover Candida species, is also helpful (3).

The dimorphic yeast of the genus Candida causes candidal infections. Candida is ubiquitous and may be present on the skin. Beyond the neonatal age, however, C. albicans is considered as part of the normal oral and intestinal flora (6). Environmental factors such as elevated temperature and increased humidity, as well as a decrease in the normal bacterial flora (e.g., due to antibiotics use) can lead to the overgrowth of the yeast. Candida albicans is the primary species that causes candidiasis in children (3). Many candidal infections clear spontaneously, and are relatively minor, such as oropharyngeal candidiasis (thrush) and candidal diaper dermatitis; however, systemic candidiasis can occur, which is serious and beyond the scope of this chapter. Chronic mucocutaneous candidiasis is due to a T-cell deficiency and a specific anergy which is also beyond the scope of this chapter.

Oropharyngeal candidiasis, also known as oral thrush, is rare in the first week of life. When it does appear in the neonate, it is most commonly acquired during passage through the birth canal from the mother's infected vaginal mucosa (vaginal candidiasis). In neonates of mothers with vaginal candidiasis, oral thrush was 35 times more common than in those of non-infected mothers (6). It was found that 20% of mothers with positive vaginal cultures had neonates with positive oral cavity cultures and 11% went on to develop oropharyngeal candidiasis (6). It is important to note that approximately 31% of women with positive vaginal cultures for C. albicans do not complain of discharge (6). Oropharyngeal candidiasis in neonates usually develops an average of 8 days after birth (6). The average interval between a positive C. albicans culture to clinical findings is about 3 days (6).

In addition to being transmitted via the birth canal, C. albicans can also be transmitted from incomplete sterilization of babies' bottle feeding or from the mother's breast. The incidence of oral thrush is higher in bottle-fed infants than in breast-fed infants (6). Neonates and young children are often affected because of the immaturity of host defenses and incomplete establishment of the gastrointestinal flora.

Oropharyngeal candidiasis (thrush) often presents as whitish patches on the tongue, gums and buccal mucosa. The soft palate, uvula and tonsils may also be involved. The patches are adherent (but can be removed revealing a erythematous base, unlike leukoplakia which is not able to be removed) and are made of epithelial cells, leukocytes, keratin, food debris and C. albicans in blastospore and pseudohyphae forms. The patient may exhibit decreased appetite and poor nursing due to pain and/or discomfort, but they are often asymptomatic. Patients taking antibiotics are at higher risk of developing thrush.

Treatment varies from no treatment, to absorbed agents and non-absorbed agents. In untreated cases in newborns, oral thrush has been found to clear on its own in 23-59 days (6). Absorbed agents, such as fluconazole and ketoconazole, are effective, but the non-absorbed (topical) agents are preferred because they are equally effective.

The classically used non-absorbed agents are gentian violet and nystatin. Gentian violet is a non-absorbed agent composed of formaldehyde and mercurochrome. It is effective in inhibiting the growth of C. albicans in the mouth, but not in the bowel. This agent is unfavorable because recurrences are common, with the additional adverse effects of ulceration and irritation of the oral mucosa, staining of tissue and clothing, and the possibility of being carcinogenic (6). Nystatin comes as a suspension. It is usually applied topically three times a day. Older children and teens can swish it in their mouth, but it should be applied with a cotton applicator onto the lesions in infants and young children. Nystatin has activity against candida only (i.e., no activity against tinea and other dermatophytes).

Newer non-absorbed agents, miconazole and clotrimazole, have also been studied. Miconazole is a first generation imidazole that has in vitro activity against yeast, dermatophytes and some Gram positive bacteria. Miconazole oral gel has been studied and found to be more effective than nystatin suspension. In a study of 183 ambulatory infants with no other underlying disease, 85% of infants treated with miconazole oral gel and 21% of infants treated with nystatin suspension were cured on day 5 (6). Miconazole has a superior cure rate and a lower rate of recurrence (6).

Candidal diaper dermatitis is a benign condition that often occurs concomitantly with oropharyngeal candidiasis. Since infants with oropharyngeal candidiasis have C. albicans in their gastrointestinal tract, they inevitably excrete it as well. Infants with oropharyngeal candidiasis have been found to have candidal diaper dermatitis in about 57% of cases (6). However, many infants have candida diaper dermatitis without thrush. Patients on antibiotics are at higher risk of developing candidal diaper dermatitis.

Candidal diaper dermatitis often presents in the perianal area as erythematous (classically described as beefy red), confluent plaques with well defined edges and a scalloped border. There are often satellite lesions (red spots), which are the primary lesions, and are

considered the hallmark of localized candidal infections. Candidal diaper dermatitis often extends to the perineum, upper thighs, lower abdomen and lower back. The diagnosis of candidal diaper dermatitis can be established by culture of the area. However in most instances, the diagnosis is made clinically by its characteristic appearance. Treatment of candidal diaper dermatitis involves topical therapy such as nystatin, miconazole or clotrimazole. These agents are usually applied with each diaper change or four times a day.

In patients that have frequent recurrences of candidal diaper dermatitis, oral therapy may be used. Since C. albicans is often harbored in the gastrointestinal tract, oral treatment along with topical treatment may be beneficial. In one study of infants less than three months of age with feces positive for C. albicans, oral plus topical nystatin was compared to oral placebo plus topical nystatin. The mycologic cure rates were the same, but oral nystatin reduced the recurrence rate to 16%, compared to 33% for topical nystatin alone (6).

Tinea versicolor is a chronic fungal infection of the stratum corneum. The dimorphic yeast, Malassezia furfur (previously known as Pityrosporum ovale and Pityrosporum orbiculare), is the infecting organism. The yeast form is present as part of the skin's natural flora, but the filamentous form is seen in the disease state. This organism is more commonly seen in areas of the skin with sebum production capabilities and infection is seen more commonly in adolescents and young adults (3). Tinea versicolor presents with a lesion of varying color depending on the individual's skin type. In lighter skinned individuals, the lesions are typically seen as reddish-brown macules with fine scales. In darker skinned individuals, the lesions may appear as hyperpigmented or hypopigmented macules. The lesions usually start in a perifollicular area then coalesce to form the macular, scaly lesions. The common locations are the neck, upper chest, upper back and upper arms. Involved areas are usually not pruritic and they do not darken after sun exposure.

The diagnosis of tinea versicolor is usually made by clinical appearance, but confirmatory evidence can be obtained with a Wood's lamp, KOH preparation, and skin biopsy. Wood's lamp examination reveals a yellowish gold fluorescence. When examining KOH prepared scrapings from the lesion, a "spaghetti and meatballs" appearance is seen. The "spaghetti" are the thick, angular hyphae and the "meatballs" are the spores. Skin biopsy with culture and periodic acid-Schiff staining for fungi may be necessary to diagnose cases with principally follicular involvement. Under examination, M. furfur is seen in the follicle.

The differential diagnosis of tinea versicolor includes dermatophytoses, seborrheic dermatitis, pityriasis alba and secondary syphilis. Post-inflammatory pigment changes, although they usually do not have scales, may mimic tinea versicolor.

The treatment of tinea versicolor involves topical and oral therapy. Topical agents include selenium sulfide suspension, sodium thiosulfate lotion, and 3-6% salicylic acid applied once or twice daily for 2-4 weeks. Imidazoles such as, miconazole, clotrimazole and ketoconazole can be used twice daily for 2-4 weeks. Terbinafine cream is also effective when used for 2-4 weeks twice a day. When topical therapy fails, oral therapy can be used. Ketoconazole, fluconazole and itraconazole are commonly used oral therapy agents.

M. furfur is a normal saprophyte of the human skin, thus it is not eradicated. Tinea versicolor infections can, therefore, recur in susceptible individuals. Some risk factors of developing a tinea versicolor infection include being in a warm, humid environment, immunosuppression, malnourishment, high plasma cortisol levels, genetic predisposition, and poor skin hygiene. In most individuals, good hygiene and a healthy diet can prevent recurrences.

Antifungal agents can be summarized as follows. Tolnaftate covers only tinea. Nystatin covers only candida. Imidazoles (clotrimazole, miconazole, ketoconazole, etc.) cover both tinea and candida. Amphotericin is generally given IV for systemic fungal or candidal sepsis or disseminated infection.

Questions

1. The most common cause of Tinea capitis in the United States is:
    a. M. canis
    b. T. tonsurans
    c. M. audouinii
    d. T. capitatans

2. True/False: Tinea Capitis, "black dot" pattern, is best diagnosed with Wood's lamp.

3. True/False: Tinea pedis is most commonly seen in infant females.

4. True/False: Oropharyngeal candidiasis and candidal diaper dermatitis often occur together because of C. albicans colonization of the gastrointestinal tract.

5. Tinea versicolor lesions appear as:
    a. Hyperpigmented macules
    b. Reddish brown macules
    c. Hypopigmented macules
    d. All of the above

6. Indicate whether the following agents are active against tinea, candida or both:
    a. tolnaftate
    b. nystatin
    c. clotrimazole
    d. miconazole
    e. amphotericin
    f. ketoconazole

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Answers to questions

1. b. T. Tonsurans is the most common cause of tinea capitis in the United States.
2. False. Tinea capitis, "black dot" pattern, is caused by T. tonsurans. This is an endothrix infection, thus would not be visible by Wood's lamp. Diagnosis is best done with KOH prep or culture.
3. False. Tinea pedis is most common in preadolescent and adolescent males.
4. True. C. albicans often colonizes the gastrointestinal tract. In 57% of patients with oropharyngeal candidiasis, candidal diaper dermatitis is also seen (6).
5. d. All of the above. Tinea versicolor lesions present differently depending on the individual's natural skin color. In light skinned individuals they often appear as reddish brown scaly lesions. In darker skinned individuals they can appear as either hyperpigmented or hypopigmented macules.

6a. tinea only.
6b. candida only.
6c. both.
6d. both.
6e. both.
6f. both.

Chapter VI.33. Necrotizing Fasciitis
Chad S.D. Sparks

This is an 11 year old, previously healthy male who presents to the office with a chief complaint of extreme pain from a 3 day old puncture wound on his right calf. He also reports fever, redness, and swelling for one day. The height of his fevers is not measured. He was given acetaminophen for fever and pain. The fever improved, but the pain has worsened.

Exam: VS T 39 degrees C, HR 132, RR 26, BP 105/78. He is alert and in obvious pain. HEENT exam is negative. Lungs are clear. Breathing is tachypneic. Heart is tachycardic, without murmurs or extra sounds. Abdomen is soft and non-tender. A round puncture wound measuring 0.3 cm in diameter is noted on his right lateral calf with erythema and edema extending distally for 3 cm. Palpation of this area results in severe tenderness. The capillary refill of the skin overlying this region is slightly delayed.

A wound culture is obtained. A CBC and blood culture are drawn. IV ceftriaxone is administered and he is admitted to the hospital. Over the next 36 hours, the skin near his wound progressively develops a bluish discoloration, blisters, and bullae. Group A-beta hemolytic streptococci (GABHS) is isolated from the wound culture and blood culture. Ceftriaxone is discontinued and he is started on IV penicillin G and clindamycin for necrotizing fasciitis (NF). On the second day of hospitalization, an MRI finds fluid in a fascial plane of the lateral compartment of the lower leg. Surgical debridement is performed and brown serous fluid is removed and cultured. The surgeon confirms the diagnosis of NF. GABHS grows from the serous fluid the next day.

He continues to require daily surgical debridement until the sixth day of hospitalization, but he slowly improves. He is discharged on day ten. Follow-up for the next month shows good recovery.

Necrotizing fasciitis (NF) is a group of infections that present in any age group as an abrupt, rapidly advancing soft-tissue infection with systemic toxicity and high mortality (1). It is characterized by microbial spread along the fascial planes into deep tissue, which results in necrosis of the superficial tissue.

The classification of NF is ambiguous because of its similarity to other syndromes and its numerous etiologies. Often, the diagnoses will overlap as infection spreads to adjacent tissue. For example, necrotizing cellulitis may involve the fascial planes secondarily or vice versa. Several studies have tried to classify NF based on anatomic location, bacterial flora, presence or absence of crepitance, and clinical progression.

NF falls under the general category of necrotizing soft tissue infection (NSTI). There are three types of NSTI: 1) NF, 2) necrotizing cellulitis, and 3) myonecrosis. However, NF is often used in clinical settings as a broadly inclusive term for overlapping types of NSTI. Clinically, there are three syndromes of NF that are often described and easy to conceptualize: Type I is polymicrobial and includes saltwater NF due mainly to marine Vibrio species. Type II is group A streptococcal NF. Type III is clostridial myonecrosis or gas gangrene (2). The most common form of NF is the polymicrobial Type I. In one pediatric study, 75% of children developed NF with polymicrobial etiology (Type I) (3). The most common species of bacteria cultured from a study of 182 subjects in Maryland were Streptococcal species, Staphylococcal species, Enterococcal species, and Bacteroides species. Anaerobes such as Clostridia were also common in type I NF and could be differentiated by gas production visible on imaging studies. The most common bacteria in type I NF is Bacteroides, which is a gram-negative anaerobic bacillus. Fournier's gangrene is a variant of polymicrobial NF usually found in the scrotum or penis of older, often immunocompromised individuals. This variant is rare in children.

Type II infection with GABHS is probably the most extensively studied type of NF and is common in children (4,5). However, Type II NF has received extra attention in the lay press recently and is referred to as the "flesh-eating" bacterial infection (6). In cases where only one bacterium was present on culture, group A beta hemolytic streptococcus (GABHS) was the most common. In addition, GABHS (also known as Strep pyogenes) has been increasing in frequency since 1990 (7,8). The reason for this increase is unknown, but it may be related to the increasing incidence of other types of invasive streptococcal infections since 1985 (9).

The invasive nature of some GABHS infections and their increasing prevalence has been linked to several virulence factors. It should be noted that NF is rare compared to the total number of non-NF GABHS cellulitis infections which are much more common. The M protein has been found responsible for protecting the bacteria from phagocytosis by polymorphonuclear leukocytes (10). There are over

80 distinct M proteins, but the two most often isolated in NF are the M-1 and M-3 subtypes of S. pyogenes (8). Another important virulence factor is the exotoxin. There are five different exotoxin proteins: A, B, C, D, and E. Most commonly noted in NF are the streptococcal (scarlatina) pyrogenic exotoxins (SPE) types A, B, and C. Exotoxins recruit T cells and increase production of tumor necrosis factor alpha, interleukin 1-beta, and interleukin 6. The effects are characterized by fever, shock, edema, and multiple organ failure (11). The streptococcal superantigen (SSA) can also play a role in this process. Although these proteins are unique to the Streptococcal species, the clinical picture is often difficult to distinguish from other types of NF (4).

Type III NF is most often associated with crepitus due to growth of clostridium perfringens. This is often referred to as gas gangrene. The gas produced can often be seen on various imaging modalities such as x-ray, MRI, or CT.

The differential diagnosis of severe pain and inflammation of the skin includes cellulitis, erysipelas, acute febrile neutrophilic dermatosis, acute hemorrhagic edema of infancy, drug reactions, and vasculitis. NF is regularly confused with cellulitis because its early clinical presentation is also pain, erythema, and edema. However, cellulitis extends only to the subcutaneous tissue and is poorly demarcated. An experienced clinician is usually able to make an accurate diagnosis. Definitive differentiation from necrotizing cellulitis is generally established with surgical incision and probing. If any question remains after probing, a biopsy should be obtained (12). Erysipelas is red, raised, well-demarcated areas of induration and usually involves only the superficial cutaneous tissue. Ecthyma gangrenosum may also present as NF, but is due to Pseudomonas and appears ulcerated rather than bullous (13).

Although there are several distinct etiologies of NF, the clinical presentations are very similar. The clinical picture of NF is significant for pain, erythema, and swelling that progressively extends from the site of trauma, surgery or other provoking insult. The clinician's history should include questions regarding any inciting event such as a small wound or traumatic occurrence at the site of infection. On the other hand, the absence of an initiating event does not rule out NF. Common initiating events depend on the age group as well as the patient's immune status. In the newborn, NF can be a serious complication of omphalitis. It may begin as swelling and erythema around the umbilicus and progress to a purplish discoloration and periumbilical necrosis during the subsequent hours or days (13). In older children, NF may present after trauma, surgery, or with resolving varicella lesions. In a study, almost 50% of pediatric cases were superimposed upon varicella in its 3rd-4th day of progression (8). The history frequently reveals a persistent fever after the third day of rash, associated with severe, localized pain, over an area of swelling, erythema, and possibly necrosing skin (14). The mechanism of how varicella increases the risk for NF is unknown. An association has been shown between NF and NSAID use with varicella. Numerous studies examined this relationship, but the results have been mixed. Most believe these studies do not prove a causal relationship. However, physicians may consider recommending acetaminophen instead of ibuprofen for children with varicella (15).

Pain in an extremity is usually the presenting symptom. It is extreme and often out of proportion with the physical findings. NF has a propensity for the extremities, but can occur anywhere there is deep fascia (16). In the first 24-48 hours, it is associated with edema, erythema, and warmth of the skin overlying the necrotizing tissue. After that point, the skin will become dusky and discolored. It will develop blisters and bulla over the next seven to ten days. During that time, the discoloration will become sharply demarcated. Its tenderness will also disappear as the superficial nerves experience ischemia (17). This progression is both faster and more severe than that seen in cellulitis or erysipelas (18). If not addressed, NF can quickly progress to multi-organ failure, acute respiratory distress syndrome, renal impairment, coagulopathy, liver abnormalities, and generalized erythroderma (19).

Although the diagnosis of NF is primarily clinical, laboratory workup and imaging may be helpful. Surgical probing and frozen section biopsy are used for diagnosis of NF, but they are invasive and take time to complete. There must be a high index of suspicion for NF to move straight to surgery. Therefore, the most important first steps of medical management are probably the gram stain and cultures of both the blood and the wound, if one is present. This will help guide antibiotic therapy over the course of the disease. In addition, routine blood work such as a CBC and chemistry panels may be helpful.

Imaging can also be very useful in differentiating NF from cellulitis. Crepitus or soft tissue gas on plain x-rays are pathognomonic for NSTI. However, they are only found in 37%-57% of the cases (20). More recently, MRI and CT scans have been investigated to identify NF. Contrast enhanced images may show asymmetric thickening of the deep fascia and/or gas bubbles in the deep tissue. However, MRI may overestimate the extent of disease and intravenous contrast may be contraindicated in some patients in shock or with renal failure. In most cases, however, empiric treatment should be initiated as soon as possible, even prior to obtaining imaging results (21).

The mainstays of treatment for NF are intravenous antibiotics and surgical debridement. Generally, broad antibiotic coverage is necessary for empiric therapy. A study by Elliot suggested a combination of ampicillin, gentamicin, and clindamycin or ampicillin/sulbactam for broad coverage (4). Penicillin covers GABHS and most anaerobes. Clindamycin covers all anaerobes and it inhibits bacterial protein (toxin) synthesis in organisms that are not multiplying. However, anaerobic infections are frequently polymicrobial necessitating broad spectrum coverage. Specific antibiotic therapy can be employed after cultures return and bacterial sensitivities are known. Recent studies indicate clindamycin treatment produces better outcomes and decreases mortality in streptococcal disease. In fact, a combination of the two drugs is currently advocated in the literature (3,22). In the pediatric setting, there is no current recommendation for length of antimicrobial treatment, but it should be continued as long as there are signs of infection. Treatment for cellulitis is continued for at least three days after the acute inflammation has subsided (22). Therapy for NF should be continued for at least as long as for severe cellulitis.

Surgical debridement is recommended every day until the patient is stable and without signs of infection or sepsis. Debridement should cover the infected area as well as a margin of healthy tissue to prevent reoccurrence of infection. As a result, the patient may need extensive skin grafting to cover the debridement area. During recovery, frequent dressing changes are necessary. Unfortunately, scarring and disfigurement are very common after NF debridement and grafting. In addition, physical therapy and rehabilitation will be needed for those with extensive skin grafts (20).

Mortality is always worse if there is significant delay in therapy or inadequate surgical debridement. Unfortunately, NF is often diagnosed at a very late stage because the clinical presentation initially appears to be an ordinary cellulitis or wound infection. Therefore, management should begin as soon as possible with intravenous antibiotics and surgical debridement.

Hyperbaric oxygen (HBO) therapy has been evaluated as an adjunctive therapy. Treatment with HBO has not been examined adequately in randomized trials, but some studies have shown benefit in preventing the extension of NF. It may accomplish this by increasing the oxygen tension in the surrounding tissue (23). In fact, HBO has become standard treatment in clostridial myonecrosis (24). Unfortunately, HBO is difficult to obtain and is rarely utilized. Other management concerns are the systemic effects of NF. Organ system problems that need to be addressed may include respiratory insufficiency, transient renal failure, and blood pressure support.

Mortality in the literature ranges from 12% with early, aggressive treatment (1) to nearly 100% for those without surgical debridement (8). Prognosis depends most heavily on the patient's age. In one study, NF patients younger than age 35 had no fatalities. In

contrast, mortality was 61% in the age group above 65 years. This difference may be explained by the various predisposing factors in the older group, such as diabetes mellitus. In fact, 62% of all NF patients had predisposing factors, but none were present in the younger group. However, the younger group was also more likely to have undergone surgery, which may indicate more intense therapy for the younger group. Other important factors impacting disease outcomes are the development of bacteremia, shock or hypotension, use of antibiotics other than clindamycin, or lack of adequate surgical debridement (8). Complications with toxic shock syndrome occurred in 50% of cases in one study (25). However, there was no correlation between increased mortality and specific M-serotype or the presence of SPE (streptococcal pyrogenic exotoxins) A or C (8).

Questions

1. The most common species of bacteria isolated from Type I NF is:
    a. Staphylococcus
    b. Streptococcus
    c. Bacteroides
    d. Clostridium

2. Which imaging modality is most useful in differentiating cellulitis from NF?
    a. Plain radiograph
    b. MRI
    c. CT
    d. Ultrasound

3. The virulence factor which has been found to protect streptococcal species from phagocytosis is:
    a. Streptokinase
    b. M-protein
    c. Streptococcal pyrogenic exotoxins
    d. Streptolysin O
    e. Hyaluronidase

4. Type III NF is most often caused by:
    a. Clostridium perfringens
    b. Group A beta-hemolytic streptococcus
    c. Bacteroides
    d. Campylobacter

5. First line treatment for streptococcal NF is:
    a. Erythromycin
    b. Gentamicin
    c. Doxycycline
    d. Penicillin

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Answers to questions

1.c. Bacteroides is the most common bacteria isolated in polymicrobial NF. Staphylococcus, streptococcus, and clostridium are also commonly found.

2.a. Plain films are routinely used to differentiate cellulitis and NF. MRI and CT are currently under investigation for utility, however, they are costly and time consuming. Answers b and c could be correct, but ultrasound (answer d) is not useful. If NF is suspected, surgical exploration is necessary and will yield the same information.

3.b. The M protein inhibits the activation of complement and prevents phagocytosis. The other virulence factors listed belong to the streptococcal species, but have different roles in causing infection.

4.a. Clostridium causes gas gangrene and crepitus, which characterizes Type III NF. The other bacteria listed are causes of Type I or Type II NF.

5.d. First line therapy for streptococcal NF is penicillin according to current guidelines. Unfortunately, one does not initially know that the NF is due to GABHS. Most anaerobes are penicillin sensitive. Adding clindamycin may be useful even if the organism is penicillin sensitive since it may inhibit protein synthesis (toxin production) in non-replicating organisms. For other organisms, anti-microbial therapy should be based on culture and sensitivity results when they are obtained.

Chapter VI.34. Lymphadenitis and Lymphangitis

Teresa M. Bane-Terakubo, MD

A 3 year old female presents to her primary care physician with a chief complaint of a neck mass that has been present and getting worse over 4 days. The mass started as a small lump that has enlarged to the size of a walnut and is now becoming painful, and warm to touch with overlying redness. She has had 2 days of fever up to 104 degrees (40 degrees C). She is also complaining of a runny nose, cough and sore throat for 1 week. Her appetite for solid foods is down but she is drinking fluids well and her urine output is normal. She has not been as active as usual and has not slept well due to the fever. No one at home has been ill but she does attend pre-school and several children have been ill recently with sore throats and URI symptoms. Her history is negative for recent skin infection, skin rash, weight loss, dental problems or cavities, nausea, vomiting or diarrhea. There is no exposure to cats or other animals. Her past medical history, family history and social history are unremarkable.

Exam: VS T 40, P 110, RR 20, BP 80/40, oxygen saturation 100% in room air. Height and weight are at the 50th percentile. She is tired appearing but in no acute distress. Pupils are equal and reactive. Sclera is white and conjunctiva are clear. TMs are normal. Her throat is erythematous with patches of exudate on both tonsils. Some clear nasal mucus is noted within her nares. Her neck is supple with tender bilateral cervical lymphadenopathy. There is a 2 cm x 3 cm tender, warm anterior cervical lymph node on the right with overlying erythema. Fluctuance is present. No axillary or inguinal lymphadenopathy is appreciated. Heart is regular without murmurs. Lungs are clear. Abdomen is nontender and nondistended. No hepatosplenomegaly or masses are noted. Her extremities are warm with full pulses and capillary refill time of one second. No skin rashes or impetigo scars are noted. Neurologic exam is normal.

A throat swab is sent for beta hemolytic strep culture. CBC shows WBC of 25,000 with a left shift. She is started on IV clindamycin empirically. An ultrasound study shows abscess formation. A surgeon is consulted and the abscess is incised and drained (I&D) for a moderate amount of pus. Gram stain shows numerous WBCs and gram positive cocci. Culture of the pus grows out Strep pyogenes (group A strep) within 24 hours. Her throat culture also grows group A strep. Her antibiotics are changed to IV penicillin. She responds to the antibiotics and I&D with dramatic improvement. She is discharged after 3 days of hospitalization to complete a 10 day course of penicillin.

Lymphadenopathy is a common complaint that brings children to see a physician. Fortunately, most of these children will have a benign, self-limited process. However, some children with serious systemic disease or malignancy may present with lymphadenopathy. It is therefore important to understand the differential diagnosis, perform a thorough history and careful physical exam and be aware of the appropriate work up to undertake in a timely manner. Enlargement of a lymph node (lymphadenopathy) may be caused by proliferation or invasion of inflammatory cells (lymphadenitis) or by infiltration of malignant cells. The location of the enlarged lymph node can be helpful in the differential diagnosis. It is normal for healthy children to have palpable lymph nodes in the anterior cervical, axillary and inguinal areas. Palpable lymph nodes in the supraclavicular region; however, often reflect mediastinal malignancy.

Important questions to ask the patient/caregiver include location and duration of the enlarged lynch node (acute vs. chronic, localized vs. generalized), history of prolonged fever, weight loss, arthralgias, skin lesions/infections or rashes, history of recurrent infections, immunization status, contact with sick persons, recent travel, exposure to animals and insects, URI symptoms, sore throat and dental problems/cavities. On physical exam, pay particular attention to location, consistency (solid or fluctuant, smooth or nodular, movable or fixed), number, distribution and size. The appearance of the overlying skin should be noted (red and warm in infection, violaceous coloration in nontuberculous mycobacteria). Hepatosplenomegaly, bruises, petechiae, conjunctivitis, pharyngitis, periodontal disease, and signs of systemic disease should be looked for.

The term "shotty" is commonly used to describe lymphadenopathy. Shotty means shot-like, which refers to bird shot (tiny beads) or buck shot (bigger beads). Shotty lymphadenopathy could refer to a matting of lymph nods with tiny bumps, medium bumps or big bumps. This term is vague and it may be preferable to use more accurate terminology.

Most patients with lymphadenopathy clinically assessed to be due to a minor infection do not require any laboratory testing. Laboratory work up to consider in a patient with a potentially more serious presentation of lymphadenopathy includes PPD, HIV screening, throat culture, CBC, blood culture. Serologic studies for EBV (Epstein-Barr virus), CMV (cytomegalovirus), HIV, Treponema pallidum, Toxoplasma gondii, or Brucella can be helpful in selected cases. For a patient with a fluctuant node where an abscess is suspected, ultrasound may be helpful. Needle aspiration of a suspected abscess may negate the need for an ultrasound but this approach is more invasive. Although a needle aspirate can yield the organism contained within an abscess, most abscesses will have to be surgically drained anyway. Occasionally, a lymph node biopsy may be needed. This tissue is usually sent for gram stain, bacterial culture, acid fast stain, mycobacterial culture, or Bartonella henselae (cat scratch disease) PCR. A chest x-ray evaluation should also be considered to rule out mediastinal masses/malignancy.

The differential diagnosis for lymphadenopathy is best based upon the presentation as either acute bilateral cervical lymphadenitis, acute unilateral pyogenic (suppurative) lymphadenitis, and chronic cervical lymphadenopathy. The most common causes of acute bilateral cervical lymphadenitis are URI viruses such as adenovirus, influenza and RSV. Viruses that typically cause generalized lymphadenopathy such as EBV and CMV may also present as acute bilateral cervical lymphadenitis. The most common causes of acute unilateral pyogenic (suppurative) lymphadenitis are Staph aureus and group A strep. Most of these children are 1-4 years of age. The typical clinical course of lymphadenitis due to group A strep, is manifested in association with group A strep tonsillitis, both of which respond to penicillin. Abscess formation and the need for surgical drainage are uncommon with group A strep. However, Staph aureus more commonly forms abscesses and I&D will almost always be necessary. If there is a prior history of dental problems or a dental abscess, anaerobic oral flora may be the cause. The differential diagnosis for chronic cervical lymphadenopathy is more extensive. The most common causes of prolonged cervical lymphadenopathy are infectious such as atypical mycobacterial infections, mycobacterium tuberculosis, cat scratch disease, EBV, CMV, toxoplasmosis, histoplasmosis and HIV. Noninfectious etiologies for chronic cervical lymphadenopathy include malignancy such as leukemia, lymphoma, metastatic solid tumors such as neuroblastoma, rhabdomyosarcoma and nasopharyngeal carcinoma. One other important etiology that does not fall into the above categories is Kawasaki disease. Kawasaki disease is associated with a single, nontender, nonpurulent enlarged cervical lymph node.

Since most cases of acute bilateral cervical lymphadenitis are viral in etiology and self -limited, only symptomatic treatment is recommended. For children with acute unilateral pyogenic (suppurative) lymphadenitis caused by Staph aureus or group A strep who do not appear toxic and have no apparent abscess or cellulitis oral empiric therapy with cephalexin, oxacillin or clindamycin is recommended. For ill appearing children who have abscess formation or cellulitis, needle aspiration or I&D and IV therapy with clindamycin or vancomycin is recommended. For children who have cervical lymphadenitis associated with periodontal disease, needle aspiration or I&D and therapy with penicillin or clindamycin are optimal. For suspected nontuberculous mycobacteria infection, surgical excision of the infected lymph node without antibiotic therapy is optimal. For cat scratch disease following needle aspiration and PCR diagnosis of Bartonella infection, no antibiotic therapy is routinely recommended, although this is controversial since azithromycin has some clinical efficacy.

The prognosis for lymphadenopathy and lymphadenitis depends upon the etiology. In general, since most childhood acute bilateral cervical lymphadenopathy is viral in etiology, the prognosis is good. Since most acute unilateral pyogenic (suppurative) lymphadenitis is caused by Staph aureus and group A strep, and is easily treatable, the prognosis is also good. Since the differential diagnosis for chronic cervical lymphadenopathy is more extensive, generalized statements about prognosis are difficult to make.

Lymphangitis is the inflammation of the lymphatic vessels. The etiology of lymphangitis can be neoplastic or benign. If the lymphatic vessels are infiltrated by tumor cells, surrounding fibrosis takes place producing visible or palpable cords. Lymphangitis is sometimes seen proximal to areas of cellulitis (especially those caused by group A strep) as red streaks extending from the cellulitis proximally. Such cases are treated similar to cellulitis alone.

Questions

1. What are the indications for biopsy of a lymph node?
2. What is the most common cause of acute bilateral cervical lymphadenopathy in children?
3. What is the most common cause of acute unilateral cervical lymphadenitis associated with fever and suppuration?
4. What is the most appropriate treatment of suppurative cervical lymphadenitis caused by nontuberculous mycobacteria?
5. What are some causes of prolonged cervical lymphadenitis in children?

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Answers to questions

1. Persistent enlargement despite empiric therapy, persistent enlargement or no improvement with negative laboratory work up, solid fixed mass, mass located in the supraclavicular area, accompanying constitutional signs of persistent fever or weight loss.
2. Self limited, systemic viral infections such as adenovirus, influenza, and RSV are most common. EBV and CMV also can present as acute bilateral cervical lymphadenitis.
3. Staph aureus and Strep pyogenes (group A strep). Suppuration is more likely to be present with Staph aureus.
4. Complete surgical excision of the node is required to avoid development of a draining fistula.
5. Nontuberculous mycobacteria and cat scratch disease are common. EBV, CMV, toxoplasmosis, histoplasmosis, HIV are other infectious etiologies. Malignant diseases such as leukemia, lymphoma and solid tumors such as neuroblastoma, rhabdomyosarcoma and nasopharyngeal carcinoma also need to be considered.

Chapter VII.1. Congestive Heart Failure
Lance K. Shirai, MD, MS

This a 6 week old female who presents to the emergency room with the chief complaints of lethargy, poor feeding, and respiratory distress. She was well until 2 weeks prior to presentation when she developed a febrile illness with cough, rhinorrhea, and emesis. She subsequently developed progressive respiratory distress. Her parents report that she sweats a lot on her forehead when feeding. Her parents have also noted her to be increasingly lethargic, with tachypnea, and retractions.

She is the product of a G3P2, full term, uncomplicated pregnancy. Delivery was unremarkable except for meconium stained fluid. She did well at delivery and in the nursery. Her pediatric follow-up has been poor.

Exam: VS T 36.8, RR 72, HR 160, BP 92/68. Oxygen saturation in room air is 99%. She is a mildly cachetic, acyanotic infant who was pale, lethargic, and tachypneic, with mild to moderate subcostal and intercostal retractions. HEENT exam is unremarkable. Neck is supple without lymphadenopathy. Her skin is clear with no rashes or other significant skin lesions. Her lungs have scattered crackles with slightly decreased aeration in the left lower lobe. The precordium is mildly active. Her heart is of regular rate and rhythm, with a Grade II/VI holosystolic murmur at the mid lower left sternal border with radiation to the cardiac apex. The S1 is normal and the S2 is prominent. An S4 gallop is noted at the cardiac apex. There are no rubs or valve clicks. Her abdomen is soft, non-distended, and non-tender. The liver edge is palpable 3 to 4 cm below the right costal margin. There are no palpable masses or splenomegaly. Bowel sounds are hypoactive. Her extremities are symmetric and cool, with peripheral pulses 1+/4+ in all extremities with no radial-femoral delay. The capillary refill is 4 to 5 seconds (delayed).

A chest x-ray shows moderate cardiomegaly with a moderate degree of pulmonary edema. There are no pleural effusions. A 12 lead electrocardiogram shows a sinus tachycardia, normal PR and QTc intervals, and a left axis deviation. Voltage evidence of biventricular hypertrophy is present. No significant Q-waves or ST segment changes are noted. An echocardiogram reveals a large perimembranous ventricular septal defect with non-restrictive left to right shunting. All cardiac chambers are dilated. Left ventricular contractility is at the lower range of normal. There is no pericardial effusion.

She is admitted to the hospital and loaded with digoxin, and also started on diuretics and afterload reduction. Her symptoms improve and she is discharged on 24 calorie/ounce formula due to poor weight gain on standard 20 calorie/ounce formula. She continues to have poor weight gain on higher caloric density formula and continues to have symptoms of heart failure on medical management. She is referred for surgical correction of the ventricular septal defect at 6 months of age.

Heart failure (or congestive heart failure) is defined as the inability of the myocardium to meet the metabolic requirements of the body. This may arise as a consequence of excessive work or volume load imposed on the myocardium, primary alterations in myocardial performance, metabolic derangements, or a combination of these elements. Heart failure leads to a neurohormonal response, which contributes to the symptoms associated with heart failure and increased morbidity and mortality.

In the pediatric age group, the underlying abnormality is often a large left to right intracardiac shunt, most commonly a ventricular septal defect, or an obstructive lesion, such as an aortic coarctation. In contrast to heart failure in adults, pediatric patients often have normal left ventricular function. Exceptions to this may include patients with myocarditis, dilated cardiomyopathy, ischemia-reperfusion injury following cardiopulmonary bypass, or a congenital coronary artery anomaly.

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Heart failure can be classified into 4 functional classes:

1) Volume overload: Large left to right shunts, valvular insufficiency, or systemic arteriovenous fistulae.

2) Pressure overload: Outflow or inflow obstruction.

3) Disorders affecting the inotropic state: Myocarditis, electrolyte disturbances, hypoxia, acidosis, various cardiomyopathies, coronary artery lesions, endocrine or metabolic derangements, septic shock, toxic shock.

4) Alterations in the chronotropic state: Supraventricular or ventricular tachycardia, complete heart block.

To better understand congestive heart failure in pediatric patients, especially infants, one must have an understanding of the developing heart. Fetal and newborn hearts function at a high diastolic volume (high on the Frank-Starling contractility curve) and therefore have limited diastolic reserve. As afterload or volume load on the young heart increases, there is relatively limited ability to develop additional contractility. This is thought to be, at least in part, due to a relative paucity of the contractile mass in the developing heart, incomplete neural innervation, and low norepinephrine stores. An increase in heart rate is the dominant mechanism to increase cardiac output in all patients with heart failure, but this is especially important in infants and younger children.

There are several neurohormonal and biochemical derangements in congestive heart failure, which perpetuates its symptomatology and leads to chronic heart failure. Alterations in calcium handling occur within the myocardium secondary to impairment of sarcoplasmic reticulum function, anaerobic metabolism, and developing acidosis. The fall in cardiac output and changes in regional circulation accompanying heart failure leads to an activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system. Activation of these systems can lead to direct myocardial toxicity, peripheral vasoconstriction, and increased renal sodium and water reabsorption. Cardiac beta-receptors are down-regulated causing a reduced inotropic response to beta-adrenergic stimulation. Myocardial remodeling including hypertrophy, cell injury, and fibrosis, interferes with normal myocyte function and increases susceptibility to arrhythmias.

Clinical findings in congestive heart failure can be broken down into signs and symptoms of impaired myocardial performance, pulmonary congestion, and systemic venous congestion.

The signs and symptoms of impaired myocardial performance include:

1) Cardiomegaly: Represents ventricular hypertrophy and/or dilatation.

2) Tachycardia: Mediated by an increased adrenergic drive. This is the body's attempt to improve cardiac output and oxygen delivery.

3) Gallop rhythm: Represents either increased flow across the AV valves in the presence of a large left to right shunt, or rapid filling of a non-compliant ventricle.

4) Atrioventricular valve regurgitation: Due to ventricular dilatation, decreased ventricular contractility, and at times infarction of papillary muscles.

5) Decreased or increased arterial pulsations depending on the lesion leading to heart failure. Extremities are usually cool, with weak peripheral pulses secondary to systemic vasoconstriction. Arterial pulses may be bounding with lesions causing a large diastolic runoff as seen with large arteriovenous fistulas, patent ductus arteriosus, or an aortopulmonary window (other aorto-pulmonary communication).

6) Growth failure: A consequence of decreased systemic perfusion and raised energy requirements.

7) Diaphoresis (especially with feeding): Represents increased adrenergic activity.

The signs and symptoms of pulmonary congestion include:

1) Tachypnea: Secondary to interstitial and bronchiolar edema.

2) Wheezing: Due to external compression on airways, e.g., from an enlarged left atrium.

3) Rales: Implies the process is severe, with involvement of the alveolar spaces.

4) Mild cyanosis: Secondary to impaired gas exchange (pulmonary edema).

5) Dyspnea.

6) Orthopnea.

7) Persistent cough.

The signs and symptoms of systemic venous congestion include:

1) Hepatomegaly: This may be associated with a mild elevation in the bilirubin level and liver function tests.

2) Jugular venous distention: Seen only in older children and adolescents.

3) Peripheral edema: Facial edema is most common in infants and children. Extremity edema may be seen in older children and adolescents. Ascites is usually only seen in older age groups with very advanced heart failure.

It must be remembered that the signs and symptoms of congestive heart failure in pediatric patients with congenital heart disease will begin at varying ages depending on whether the patient has a ductal dependent lesion or a left to right shunt. Patients with large left to right shunts, such as those with a large ventricular septal defect or atrioventricular canal, may not present with symptoms until 4 to 6 weeks of age when the pulmonary vascular resistance has decreased sufficiently to allow development of interstitial and alveolar pulmonary edema. Ductal dependent lesions (e.g., hypoplastic left heart syndrome, aortic coarctation, pulmonary atresia) most often will present in the newborn period as cyanosis. Occasionally these patients will not present until 1 week or more of life after the ductus arteriosus has closed and the patient presents in a shock-like state.

There are several laboratory studies utilized in the diagnosis and assessment of congestive heart failure in the pediatric patient. A chest x-ray is one of the more useful studies in the initial assessment of a patient with suspected heart failure. This allows evaluation of heart size and contour, pulmonary vascularity, presence of pleural effusions, abdominal and cardiac situs (i.e., whether situs inversus or dextrocardia is present), aortic arch sidedness (occasionally, since the X-ray sign of a right or double aortic arch is very subtle), and lung expansion. An electrocardiogram is most useful in instances where heart failure is secondary to an arrhythmia, anomalous coronary artery, or myocarditis. Echocardiography is useful in all patients with heart failure to assess for structural anomalies, cardiac function, and cardiac chamber sizes. Since filling chamber enlargement is one of the initial abnormalities in heart failure, the earliest sign of heart failure will be cardiomegaly (before pulmonary edema) on chest x-ray (CXR), and the earliest sign of heart failure on an echocardiogram will be enlargement of the filling chambers (left atrium for left sided heart failure, right atrium for right sided heart failure) and/or decreased ventricular contractility.

Other useful laboratory studies may include an arterial blood gas (in very ill patients), serum electrolytes (including calcium and magnesium levels), and a complete blood count (to help rule out the presence of anemia). Pediatric patients with heart failure will often have a mild hyponatremia, resulting from increased renal water retention rather than a true negative sodium balance. Mild hyponatremia, therefore, does not need to be treated. Administering supplemental sodium may actually worsen the patient's fluid retention and heart failure.

The major goals in the treatment of congestive heart failure include relief of pulmonary and systemic venous congestion, improvement of myocardial performance, and reversal of the underlying disease process (if possible). Historically, digoxin has been one of the most widely used pharmacologic agents in the treatment of heart failure in infants and children. In addition to its positive inotropic effect, digoxin exerts beneficial effects via sympathetic-inhibiting actions via baroreceptor, central, and adrenergically mediated mechanisms. Other inotropic agents used in the treatment of acute heart failure include dopamine, dobutamine, and phosphodiesterase inhibitors (milrinone and amrinone).

Diuretic therapy plays an integral part in the treatment of pediatric patients with congestive heart failure. The three most commonly utilized classes of diuretics include the loop diuretics (furosemide-Lasix, bumetanide-Bumex), potassium sparing diuretics (spironolactone), and thiazide diuretics (hydrochlorothiazide). The benefits of diuretic therapy include improvement in systemic, pulmonary, and venous congestion. Spironolactone may exert additional beneficial effects by attenuating the development of aldosterone-induced myocardial fibrosis, and catecholamine release. This currently remains under investigation. Potential complications of diuretic therapy include volume contraction, electrolyte abnormalities (hyponatremia, hypo- or hyperkalemia, hypochloremia), and metabolic alkalosis or acidosis. Electrolyte balance should be carefully monitored, especially during aggressive diuresis, as the failing myocardium is more sensitive to arrhythmias induced by electrolyte dyscrasias.

The use of afterload reduction is one of the newer concepts in the management of heart failure. Relaxation of arteriolar smooth muscle helps to decrease the systemic vascular resistance and augment cardiac output. Venodilatation exerts its effect on preload by increasing venous capacitance, thus lowering filling pressures. The angiotensin-converting enzyme (ACE) inhibitors decrease systemic vascular resistance and have a favorable effect on the body's neurohormonal response to heart failure and cardiac remodeling. Several adult studies have demonstrated improved symptoms and survival with the use of ACE inhibitors in patients with heart failure. Their role in the treatment of heart failure in children is less well defined. They are thought to have beneficial hemodynamic effects in patients with decreased systemic ventricular contractility, and those patients with large left to right shunts. ACE inhibitors should be started at a low dose then gradually increased, especially in infants. The phosphodiesterase inhibitor milrinone is often used in the intensive care setting of acute, new onset systemic ventricle dysfunction (e.g., myocarditis), and in the immediate post-operative setting following cardiopulmonary bypass (ischemia-reperfusion injury).

Treatment of chronic heart failure with the use of beta-blockers, such as carvedilol, is now an accepted practice in the adult population. Several studies have shown a reduction in both hospitalization and mortality. The beneficial effects are thought to be derived

from the reversal of myocardial dysfunction occurring secondary to sympathetic activation and down-regulation of beta-adrenergic receptors, coronary artery vasodilatation, and possible anti-oxidant effects. The present state of knowledge for use in the pediatric population is based on anecdotal experience from unblinded, non-randomized studies of small sample size. Therefore, beta-blockers should be used with caution in infants and children with chronic heart failure until more experience is gained with these agents.

Other non-pharmacologic therapeutic measures that may be considered in patients with congestive heart failure include elevation of the head and shoulders to 30 to 45 degrees, bedrest, dietary changes (higher caloric intake, and a low sodium diet in older children and adolescents), packed red blood cell transfusion, iron supplementation, and the administration of supplemental oxygen. It must be remembered that oxygen is a pulmonary vasodilator, therefore in patients with known large left to right shunt lesions, administration of oxygen will decrease pulmonary vascular resistance, increase the degree of left to right shunting, and worsen the degree of pulmonary edema.

For acute pulmonary edema, several treatment methods are used which help to understand the underlying pathophysiology. Within the alveolus, the major force which holds water in the interstitial and vascular space is the plasma oncotic pressure. The force attempting to push water out into the alveolar space is the hydrostatic fluid pressure. Pulmonary edema basically occurs when the hydrostatic force pushing the fluid out, exceeds the oncotic force holding the fluid in. The air pressure within the alveolus has some effect as well. It is slightly positive (pushing the fluid out of the alveolus into the interstitium) when we exhale, since we exhale against partial resistance. The air pressure is negative when we inhale (which favors drawing fluid into the alveolus). To treat acute pulmonary edema, the hydrostatic force pushing the fluid out into the alveolar space can be reduced by reducing back pressure (preload and afterload reduction) by the following therapeutic measures: 1) diuresis, 2) vasodilation (increases vascular capacitance), and 3) augmenting contractility (reduces back pressure). An alternative means to treat acute pulmonary edema is to increase the pressure within the alveolus to counterbalance the excessive hydrostatic pressure with positive pressure ventilation via mask CPAP (continuous positive airway pressure) or through an endotracheal tube with a ventilator. This literally pushes the fluid out of the alveolus back into the interstitium and vascular space. The most important parameter to increase to reverse pulmonary edema is the PEEP, which is the positive end-expiratory pressure. With a ventilator, inspiration is under positive pressure driving the fluid out of the alveolar space. However, during exhalation, the positive pressure declines permitting the fluid to return. A high PEEP (10 to 20 mmHg) will prevent this and keep the lungs clear until other measures can be taken to control the pulmonary edema.

Other measures of historical interest only, include phlebotomy (to balance the humors) and rotating tourniquets. These measures are not as effective as the other therapies mentioned.

In patients with heart failure, the treatment plan should ultimately deal with the underlying condition. This may include surgical repair of a shunt lesion or valvular anomaly, interventional cardiac procedures, radiofrequency ablation, control of hypertension, anti-inflammatory treatment for rheumatic carditis, pacemaker implantation, carnitine supplementation, adenoidectomy and weight loss for patients with airway obstruction, pulmonary hypertension and right heart failure, or cardiac transplantation.

The prognosis of the pediatric patient with heart failure depends largely on the primary condition. In those patients with large left to right shunts, such as a ventricular septal defect, medical therapy will often maintain the patient in a well compensated state until the VSD spontaneously begins to close or it is decided the defect needs to be surgically repaired. Repair of congenital heart defects with large left to right shunts (VSD, ASD, AV canal), or those with valvular abnormalities carry a low surgical mortality in the hands of an experienced pediatric cardiovascular surgeon. The majority of patients with myocarditis, who present in heart failure, will improve with medical management. Patients with cardiomyopathies or hypoplastic left heart syndrome will occasionally require a heart transplant as a last resort. In these cases, the prognosis is much more guarded. Those patients with arrhythmia induced heart failure will often respond well to anti-arrhythmic therapy and/or electrophysiology study and radiofrequency ablation.

Questions

1. What is the most common congenital heart defect with a left to right shunt causing congestive heart failure in the pediatric age group?
    a. Atrial septal defect
    b. Atrioventricular canal
    c. Ventricular septal defect
    d. Patent ductus arteriosus
    e. Aortopulmonary window

2. True/False: Jugular venous distention is a common finding in infants with heart failure.

3. What is the most likely age an infant with a large ventricular septal defect will begin manifesting symptoms of congestive heart failure?
    a. 1 day
    b. 1 week
    c. 1 month
    d. 6 months
    e. 1 year

4. True/False. Administration of supplemental oxygen to a child with a large left to right shunt lesion will help improve the degree of congestive heart failure.

5. What is the dominant mechanism with which infants and young children increase their cardiac output?
    a. By increasing ventricular contractility
    b. By increasing heart rate
    c. By increasing ventricular end-diastolic volume
    d. By decreasing heart rate
    e. By increasing respiratory rate

6. True/False: All neurohormonal and sympathetic responses of the body to heart failure are beneficial.

7. The earliest sign of congestive heart failure on a chest X-ray is:
    a. Increased heart size.
    b. Kerley B lines.
    c. Central pulmonary vascular congestion.
    d. Pulmonary edema.
    e. Pleural effusion.

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Answers to questions

1.c, 2.False, 3.c, 4.False, 5.b, 6.False, 7.a

Chapter VII.2. Acyanotic Congenital Heart Disease

Edgar C.K. Ho, MD

A 4 year old male presents in the office for a preschool physical examination. In the course of the interview, his mother mentions that he seems to get short of breath with exercise recently. It is especially noticeable during his swimming lessons when he tires before the other children do in his class. He has otherwise been in good health since his last physical exam in the previous year. His records for the past year show 3 office visits for minor upper respiratory illnesses, and no emergency room visits. He has never had wheezing during his colds.

Exam: T37.5, P92, R25, BP right arm 97/70, oxygen saturation 98% in room air. Height and weight are at the 25th percentile. He is cooperative and well nourished in no distress. HEENT and neck exams are normal. His chest is symmetrical. Heart: No palpable thrill, normal 1st and 2nd heart sounds; no clicks or rubs; grade 1/6 ejection systolic murmur heard along the left sternal border with radiation to the back between the scapulae; no diastolic murmur. Lungs are clear to auscultation. Abdomen without no organomegaly or masses palpable. Genitalia: normal male. Extremities: Femoral pulses are slightly diminished to palpation; no peripheral edema, clubbing or cyanosis of the nail beds. His neurological is normal.

He receives his immunizations, and tuberculin skin test, and because of the new onset heart murmur, a chest x-ray and EKG are ordered. He returns in 3 days to have his skin test read and to review his cardiac tests. Before entering the exam room the nurse remeasures his vital signs and records in his chart: BP left arm 127/86, P88, R24. His chest x-ray shows a cardiac/thoracic ratio of 0.55, normal cardiac configuration, and normal pulmonary vasculature. His EKG has tall R waves of 40 mm in lead V5, and 35 mm in lead V6. An echocardiogram is performed the following day and demonstrates a coarctation of the aorta, and bicuspid aortic valve. A MRI shows a discrete narrowing of the distal aortic arch just beyond the origin of the left subclavian artery and also reveals an aberrant right subclavian artery originating from the proximal descending aorta below the coarctation.

Coarctation of the aorta is classified as an acyanotic congenital heart defect and belongs to that group of cardiac anomalies that is the result of abnormal fetal cardiac formation, that does NOT cause shunting of blood from the venous to the systemic side of the heart (i.e., it does NOT cause right to left shunting), and that may be manifested and clinically detectable some time after birth. With the advent of fetal echocardiography, these lesions are sometimes detected before birth.

A list of the acyanotic lesions can be made by enumerating the structures encountered by the flow of blood through the different parts of the heart beginning with the venous side. The most common anomalies would thus include: tricuspid valve stenosis/regurgitation, Ebstein's anomaly of the tricuspid valve (can be cyanotic in infants), pulmonic valve stenosis/regurgitation, subvalvular and supravalvular pulmonic stenosis, partial anomalous pulmonary venous drainage to the right side of the heart, atrial septal defect (secundum, primum, sinus venosus), mitral valve stenosis/regurgitation, ventricular septal defect, aortic valve stenosis/regurgitation, subvalvular and supravalvular aortic stenosis, patent ductus arteriosus, and coarctation of the aorta.

Acyanotic congenital lesions account for 70% of all congenital heart disease, the most common of which, as isolated lesions, are ventricular septal defects (most common), patent ductus arteriosus, atrial septal defect and pulmonic stenosis. Coarctation of the aorta accounts for (6%) of all congenital heart disease (1). Patients with Turner syndrome have coarctation more commonly than the general population.

Coarctation of the aorta results from constriction of the tissue of the distal aortic arch at the junction with the descending aorta and near the insertion of the ductus arteriosus. Various theories have been proposed to explain this maldevelopment. One popular theory associates the presence of ductal tissue encircling the aorta at the site of the coarctation suggesting a constrictive effect of the ductile tissue (2).

Although present at birth, coarctation of the aorta may not cause symptoms until early childhood and sometimes not until late childhood, depending on the severity of the coarctation, and the presence of associated cardiac lesions. If a ventricular septal defect is also present and is large, the coarctation of the aorta will cause increased left to right shunting across the defect, producing congestive heart failure within the first few months of life as the pulmonary resistance decreases after birth. A patent ductus arteriosus located proximal to

the coarctation would likewise increase pulmonary shunting through the ductus resulting in congestive heart failure. If the ductus is located distal to the coarctation, signs and symptoms may be delayed.

Other anomalies associated with aortic coarctation include a bicuspid aortic valve (85%) (3) that may obstruct left ventricular output, and an aberrant origin of the right subclavian artery distal to the coarctation (1%) (4). The latter will cause the blood pressure of the right arm to be equal to the leg, and may mislead one from the correct diagnosis. It is important to measure the blood pressure in both arms and at least one leg in order to detect the blood pressure differential caused by an aortic coarctation.

If coarctation of the aorta is an isolated lesion, the typical symptoms may include: shortness of breath with exertion, leg pain with exercise, and rarely, chest pain with exercise. Physical findings include: upper extremity hypertension with a blood pressure differential between arm and leg (obtain BP in both arms and one leg), a systolic murmur heard along the left sternal border and especially well over the back between the scapulae, and diminished and delayed pulses in the lower extremities when compared with the upper extremities. A chest x-ray may display cardiomegaly with a left ventricular hypertrophy configuration. In long standing cases, rib notching due to erosion of the lower anterior portion of the rib by dilated collateral arteries can be appreciated. The echocardiogram demonstrates narrowing of the distal aortic arch with increased velocities on pulsed and color Doppler. The pulsed Doppler waveform has a typical prolonged systolic phase extending throughout systole. The MRI produces a static but clearer picture, than the echocardiogram, of the anatomy of the coarctation. An angiogram is sometimes necessary to clarify associated cardiac lesions.

There are several surgical techniques used to repair a coarctation of the aorta. Each technique has had its own proponents at one time or another. If the coarcted segment is short and discrete, resection and end to end anastomosis of the proximal and distal ends is possible. If the coarctation is a long tubular obstruction, resection with interposition of a tube graft would be necessary. Some surgeons favor a longitudinal incision with insertion of a synthetic graft to enlarge the diameter. In the young infant, sacrificing the left subclavian artery, and using the transected blood vessel as a graft by turning it down and sewing it into the aortic wall was popular at one time (5).

Catheter balloon dilatation of native coarctations has not been as successful as dilatation of postoperative restenosis of a coarctation. The former technique has resulted in late appearance of aneurysms. The use of stents to reinforce the arterial wall is now preferred to balloon dilation alone.

A postoperative complication that is now rare is the syndrome of mesenteric arteritis (6), caused by reflex spasm of mesenteric arteries that are suddenly exposed to higher pressures after the coarctation is removed. The spasm can be severe enough to result in bowel ischemia. Patients are being operated on at a younger age now so that the mesenteric arteries do not have as long a period of exposure to low pressures and are therefore less reactive.

Ventricular septal defects (VSD), atrial septal defects (ASD), and patent ductus arteriosus (PDA) account for a large percentage of all congenital heart defects. They share common physiologic hemodynamics and will be discussed together.

These defects represent abnormal communications between the high pressure left side of the heart and the low pressure right side of the heart. The pressure differential results in a left-to-right shunting of blood through the defect. The consequences of this shunting of blood are: turbulence of abnormal blood flow producing a heart murmur in systole and sometimes in diastole; excessive blood flow into the lungs causing shortness of breath and increased pulmonary vascularity on a chest x-ray; and increased volume overload of the myocardium resulting in hypertrophy of myocardium and chamber dilatation.

The murmur of a VSD is located at the lower left sternal border and is dictated by the anatomic location of the defect in relation to the chest wall. Since flow across the VSD occurs as long as there is a pressure differential between left and right ventricles, the timing of the murmur in this lesion is pansystolic. The high pressure turbulence of the shunted blood produces a harsh quality to the murmur. When the pulmonic flow exceeds the systemic flow by a ratio of 2:1, an apical diastolic murmur is produced due to excessive flow during recirculation across the mitral valve. Frequently, a VSD murmur is not heard at birth (day 1 of life) since pulmonary vascular resistance and pulmonary pressure may still be high, limiting left to right shunting through the VSD. As pulmonary vascular resistance drops further, more left to right shunting through the VSD occurs, making the murmur audible on day 2 or day 3 of life.

The murmur of an ASD is produced by excessive flow across the pulmonic and tricuspid valves resulting in a systolic murmur at the second left intercostal space and a mid-diastolic murmur over the lower right sternal area. Note that this is a flow murmur and NOT a murmur due to turbulent flow across the ASD. Flow across the ASD is low velocity and not turbulent and therefore produces no audible murmur itself.

The flow through a PDA is continuous due to the existence of a constant pressure differential between aorta and pulmonary artery in both systole and diastole. The machinery quality of the murmur results from the rhythmic variation of the pressure differentiation during the cardiac cycle. The location of the murmur is at the upper left sternal border.

A small shunt produces only a murmur but no symptoms. With increasing defect size and pulmonary flow, signs and symptoms of congestive heart failure occur: shortness of breath with exertion and in severe cases, also at rest; cough and susceptibility to pulmonary infections; hepatomegaly, splenomegaly, and lower extremity edema result from retrograde extension of the systemic venous congestion into the liver, spleen and legs.

The chest x-ray in a left-to-right shunt lesion will demonstrate congested pulmonary vessels. Enlargement of specific cardiac chambers is due to excessive volume overload. The left atrium and ventricle are dilated in VSD and PDA, and the right heart chamber is dilated in ASD. The EKG reveals hypertrophy of the corresponding cardiac chambers.

Untreated defects with large shunts will eventually result in injury to the pulmonary arterioles, vascular obstruction, and pulmonary hypertension. The development of permanent injury to the pulmonary vessels is a function of the duration of the exposure to excessive blood flow and the anatomy, occurring more rapidly in VSD and PDA than in ASD. If this process is not reversed, Eisenmenger's complex of right to left shunting may occur as the right sided pressures (pulmonary hypertension) exceeds left sided pressures.

Intracardiac repair of a VSD and ASD require cardiopulmonary bypass. Repair of a PDA is extracardiac and is achieved without cardiopulmonary bypass. The intracardiac defects can be closed by primary suturing of the edges of the defect if small, or by covering with a patch material if large. The PDA is usually tied off and divided.

Complete heart block secondary to injury to the conduction system during repair of a VSD may require a pacemaker in the postoperative period. The knowledge of the location of the conduction system in relationship to the defect now makes this a rare complication. The mortality rate in experienced hands should be less than 5% if all ages are considered, with infants carrying a higher mortality rate especially if pulmonary hypertension is present.

Questions

1. True/False: Congenital heart disease is always detectable at birth.
2. True/False: Equal blood pressures in the right arm and left leg rule out the diagnosis of coarctation of the aorta.
3. Which are the three most common acyanotic congenital heart lesions?
4. True/False: The presence of palpable femoral pulses rules out the diagnosis of aortic coarctation.
5. True/False: Surgical repair of PDA does not require cardiopulmonary bypass.
6. Explain how a child with an isolated VSD (classified as an acyanotic lesion) could become cyanotic?
7. True/False: Medical students and residents will typically not hear the murmur of a VSD during the initial newborn assessment in the nursery because the murmur of a VSD is subtle and low pitched.

Related x-rays

Aortic Coarctation: Goto CS. Wheezing and Respiratory Distress in a 7-Week Old. In: Yamamoto LG, Inaba AS, DiMauro R. Radiology Cases In Pediatric Emergency Medicine, 1995, volume 2, case 6. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v2c06.html

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Answers to questions

1. False. The physiologic pulmonary hypertension present in a newborn can prevent blood flow across a septal defect or PDA. These can be detected several hours after birth or several days after birth. Other congenital heart disease lesions may remain occult for longer period of time.
2. False. An aberrant right subclavian artery originating below a coarctation will produce equal pressures in the right arm and leg.
3. VSD, ASD, PDA. Of these, VSD is the most common.
4. False. Development of collateral vessels to the lower body can produce palpable femoral pulses.
5. True.
6. Congestive heart failure and pulmonary edema may cause hypoxia. If the hypoxia is severe enough, visible cyanosis will result, although this can be overcome with oxygen and other treatments for pulmonary edema and congestive heart failure. Long standing excessive pulmonary blood flow leads to pulmonary hypertension and Eisenmenger's complex, right to left shunting and cyanosis.
7. False. They cannot hear the murmur of a VSD on day 1 because on day 1, pulmonary vascular resistance is still high, which restricts left to right flow through the VSD. On day 2, pulmonary vascular resistance is lower, so left to right shunting through the VSD increases making the murmur louder.

Chapter VII.3. Cyanotic Congenital Heart Disease
D. Venu Reddy, MD, MPH

This is a 3 month old male infant who presents to the emergency department with a history of having episodes of excessive crying followed by limpness, cyanosis and fainting. He was born at 41 weeks of gestation by C-section because of failure to progress to a 23 year old mother G1P0. Apgar scores of 7 and 8 at 1 and 5 minutes, respectively. He had a two vessel cord and acrocyanosis. His cyanosis increased with crying and he had a grade 3/6 ejection systolic murmur along the upper left sternal border (ULSB). His oxygen saturations were 95% and stable. He was discharged from the hospital and followed in the office until this episode. He is now being hospitalized.

Exam: VS T 37, P164, RR 64, oxygen saturation 83% on oxygen by nasal prongs. Weight 50th percentile. He is alert and active in mild respiratory distress, with visible cyanosis. HEENT exam is negative. His heart rhythm is tachycardic. He has a mild right precordial heave with a grade 3/6 ejection murmur at ULSB and a diminished 2nd heart sound. His lungs are clear. Liver and spleen are not enlarged. He has normal peripheral pulses with cyanotic nail beds and mucous membranes.

An echocardiogram is obtained which identifies cyanotic congenital heart disease. This is confirmed at cardiac catheterization. He subsequently undergoes palliative surgery with improved oxygenation and appearance of a continuous murmur. He is discharged in stable condition to be followed on an outpatient basis and to undergo further corrective surgery at a later date.

Cyanosis is a bluish discoloration of skin and mucous membranes. It results from reduced hemoglobin in blood of at least 3-5 gm/dL (1). Cyanosis can be secondary to cardiac, respiratory, hematologic and metabolic causes. Methemoglobinemia, decreased alveolar hypoventilation secondary to depressed respiratory center or obstruction of the respiratory passages, polycythemia, and hypoglycemia, shock, and sepsis may also cause cyanosis, or at least something that resembles cyanosis. It can be central or peripheral. Peripheral cyanosis is secondary to low cardiac output, in which acrocyanosis usually occurs with cool extremities and small pulse volume with bluish discoloration at the tip of the nose and fingers, and less in the mucous membranes. It is often difficult to differentiate pulmonary from cardiac causes of cyanosis in the newborn. A hyperoxy test may be helpful, whereby an arterial pO2 is measured in room air, which is then compared to a arterial pO2 measured in an FiO2 of about 90%-100% for about 10-15 minutes. Respiratory problems with alveolar hypoventilation usually improve with paO2 measurements well above 100-150 mmHg, whereas in right-to-left shunt cardiac lesions, the improvement in arterial pO2 is very minimal. Echocardiogram and chest x-ray are useful in differentiating these causes.

The above mentioned case represents a diagnostic and management problem. Classifying cyanotic congenital heart defects into those with increased vascularity with an accentuated second heart sound and those with decreased blood flow with a diminished second heart sound, can simplify the differential diagnosis to an extent. Chest x-ray findings and attention to the second heart sound may help. Lesions with increased or normal blood flow with accentuated second heart sounds include transposition of the great vessels, truncus arteriosis, total anomalous pulmonary venous return, single ventricle, single atrium, and hypoplastic left heart. Eisenmenger syndrome also falls into this category, but this is an acquired condition in which a patient with a left-to-right shunt and chronic CHF develops pulmonary hypertension and a subsequent right-to-left shunt. Those lesions with decreased blood flow and diminished second heart sound include tetralogy of Fallot or tetralogy of Fallot-like lesions, pulmonary atresia, tricuspid atresia, and Ebstein's malformation.

Transposition of the great vessels is the most common cyanotic congenital heart disease in the newborn infant (tetralogy of Fallot is more common overall, but many tetralogy of Fallot cases present after the newborn period). Transposition represents 4%-5% of all congenital heart defects (2). The aorta arises from the right ventricle and pulmonary artery from the left ventricle, with the aorta positioned anterior and to the right of the pulmonary artery. It is incompatible with life unless a communication exists between systemic and pulmonary circulation, as the two circulations are in parallel (and independent). During the newborn period, the PDA and patent foramen ovale (PFO) maintain this communication. As the PDA starts to close and the PFO by itself is inadequate in size, the patient develops intense cyanosis, and the patient becomes tachypneic. On auscultation, the second heart sound is greater in intensity, as the aortic valve is anterior. A heart murmur may not be present unless other associated lesions are present. An electrocardiogram may show right ventricular hypertrophy, but this is non-specific since RVH is present in normal newborns. Chest x-ray shows increased pulmonary vascular markings and a narrow mediastinal shadow secondary to a small thymus, sometimes giving the appearance of "egg on side" or "apple on a string" appearance. Echocardiography confirms the diagnosis and delineates the other associated lesions. Inadequate mixing between systemic and pulmonary circuits represents a medical emergency and a prostaglandin E1 infusion which maintains ductus arteriosus patency (to preserve mixing) may be lifesaving, followed by balloon atrial septostomy (Rashkind procedure). Surgical management consists of an arterial switch procedure (aorta and pulmonary artery are anastomosed to the correct ventricle), which is the operation of choice. The atrial switch (atrial baffling) such as Senning or Mustard procedures are no longer done because of the development of later complications. Survival without surgery is unlikely. The arterial switch procedure offers the best prognosis with a mortality of about 5%.

Tetralogy of Fallot constitutes 4%-9% of congenital heart disease and is the most common cyanotic congenital heart disease when considering all age groups together. Tetralogy of Fallot and pulmonary atresia with ventricular septal defect consist of: a) ventricular septal defect, b) pulmonary stenosis, c) overriding of the aorta, and d) right ventricular hypertrophy. Approximately 25% have a right-sided aortic arch, and about 4% have a coronary artery anomaly. The degree of cyanosis depends on the degree of pulmonic outflow obstruction. This is quite variable, from a slight obstruction, to severe obstruction with pulmonary atresia. Pulmonary atresia constitutes about 18% of the children with tetralogy of Fallot (3). The major right ventricular outflow obstruction in tetralogy of Fallot is infundibular stenosis. With mild stenosis, there may be congestive heart failure in infancy, also known as "pink tetralogy of Fallot." As infundibular stenosis increases, progressive cyanosis develops (due to less pulmonary blood flow), and infants and children may develop cyanotic or hypoxic spells, which consist of sudden onset of increased cyanosis, excessive crying, hypoxemia, acidosis, dyspnea, fainting, rarely seizures, and occasionally death if untreated. During these episodes (called "Tet" spells), there is increased right-to-left shunting (with less pulmonary flow), and decreased systemic vascular resistance. Older infants and children may assume a squatting position during playtime or long walks which increases systemic vascular resistance and decreases right to left shunting, increasing their oxygenation.

Clinical examination shows a loud systolic ejection murmur from the right ventricular outflow obstruction at the left sternal border conducted to the upper sternal border towards the suprasternal notch. The second pulmonary sound may be diminished, but the aortic component may be loud, as the aorta is anterior.

The electrocardiogram shows the non-specific right ventricular hypertrophy. Chest x-ray shows decreased pulmonary vascular markings (reduced pulmonary perfusion) and right ventricular hypertrophy with a leftward apex. There is an absence or decreased main pulmonary artery segment, which may give the appearance of a "boot shaped heart." Echocardiography demonstrates a ventricular septal defect with an overriding of the aorta, pulmonic stenosis, right ventricular hypertrophy, and in about 25% of cases, a right aortic arch (i.e., the aorta goes over the right mainstem bronchus instead of the left) is also present. Cardiac catheterization is done in cases in which the anatomy of the defect is not clear on echocardiogram.

Management during the newborn period consists of administration of prostaglandin E1 when the infant is markedly cyanotic and pulmonary blood flow is ductus dependent. This is followed by a systemic artery to pulmonary artery shunt (Blalock-Taussig shunt). Treatment of hypercyanotic spells is directed towards improving pulmonary blood flow. These include oxygen, knee/chest position, morphine, intravenous fluids, sodium bicarbonate, propranolol (beta-blocker), or increasing systemic vascular resistance by administration of drugs, such as phenylephrine. Total surgical correction of the defect is performed under cardiopulmonary bypass, and it can now be performed in young infants from 3-6 months of age or earlier (4). Prognosis is good with total correction. However, the majority of them still have residual defects and some of them may need reoperation and life long medical follow up.

Truncus arteriosus consists of a single arterial vessel arising from the heart, positioned over a ventricular septal defect, supplying systemic, coronary and pulmonary circulations. It accounts for about 1%-4% of the congenital heart defects. Associated anomalies are common, such as DiGeorge syndrome. Symptomatology depends upon the amount of pulmonary blood flow. With increased blood flow, symptoms of congestive heart failure such as tachypnea, cyanosis, retractions, etc., develop. There may be a systolic murmur at the left sternal border or an apical aortic ejection click. A diastolic murmur of truncal insufficiency may be heard along the left sternal border. The electrocardiogram may show right or left or combined ventricular hypertrophy. Chest x-ray shows an enlarged heart and increased pulmonary vasculature. There may be a right aortic arch (25%). The echocardiogram shows a truncal root overriding VSD, and pulmonary arteries arising from the trunk. Cardiac catheterization may be indicated when the anatomic features are not clear on echocardiography. Management consists of treatment of congestive heart failure followed by surgery. Surgical correction consists of closure of the VSD, separation of the pulmonary arteries from the trunk and anastomosing them through a conduit from the right ventricle (Rastelli procedure). The prognosis is poor in untreated cases. After surgery, they will need long term follow up as they will eventually need to have the conduit graft replaced.

Total anomalous pulmonary venous return (TAPVR) occurs in about 1%-2% of patients with congential heart disease. There are four types of TAPVR causing left-to-right shunt: Supracardiac, cardiac, infracardiac, and mixed. In the supracardiac type, pulmonary veins join to form a common vein which drains into the SVC. In the cardiac type, the common pulmonary veins drain into the right atrium directly or via the coronary sinus. In the infracardiac type, the common pulmonary vein courses downward through the diaphragm into the portal vein, which then drains via hepatic veins into the inferior vena cava.

Anomalous pulmonary venous return could be total or partial. An atrial septal defect is necessary for survival, since the oxygenated blood (from the pulmonary veins) must somehow reach the left side of the heart. Symptomatology depends on the amount of mixing and whether or not the pulmonary veins are obstructed. Cyanosis and signs and symptoms of congestive heart failure develop and progress rapidly. There may be a grade 2/6 systolic ejection flow murmur heard along the left sternal border, or it may be absent. The electrocardiogram shows right ventricular hypertrophy and right atrial hypertrophy. Chest x-ray shows increased pulmonary vascular markings or even edema, and the heart may be normal in size or minimally enlarged. The echocardiogram may show right ventricular volume overload, and a color-flow Doppler study may help in locating the common pulmonary venous channel and its drainage. If the resolution is poor, cardiac catheterization and angiocardiography may help in delineating the anomaly further. Treatment consists of correction of the defect by surgery. If surgery is delayed and there is inadequate mixing, palliative balloon septostomy may be performed. Prognosis is good after surgery. Prognosis is poor in neonates with obstructive TAPVR. Long term follow up is needed to assess restenosis and late arrhythmias.

Tricuspid atresia consists of an absence or atretic tricuspid valve and a hypoplastic right ventricle. Blood from the right atrium enters the left atrium through an atrial septal defect or foramen ovale. They may have associated lesions such as TGA, VSD, PDA, right aortic arch, pulmonic stenosis or atresia. Communication between right and left circulation is essential to sustain life. Symptomatology depends on the amount of pulmonary blood flow. In the absence of a VSD, as the PDA closes, patients may develop intense cyanosis, tachypnea and tachycardia. The electrocardiogram usually shows left axis deviation (very unlike the RVH seen in normal newborns) and right atrial hypertrophy and left-ventricular hypertrophy. Chest x-ray may show increased or decreased pulmonary blood flow depending on the shunt and a normal or mildly increased heart size. Echocardiography usually delineates these abnormalities and very rarely a cardiac catheterization may be needed. Prostaglandin E1 may be life saving in infants with low oxygen saturation with duct dependent pulmonary blood flow. This is followed by a modified Blalock Taussig anastomosis. If the interatrial communication is narrow (small PFO/ASD) then a balloon or blade atrial septostomy is performed (5). Surgical correction initially consists of a bilateral Glenn procedure (superior vena cava to right pulmonary artery shunt) followed by an inferior vena cava anastomosis to the right pulmonary artery through an intra or extra cardiac baffle (modified Fontan procedure). Prognosis is good after surgery but patients will need multiple surgeries with associated morbidity such as pleural effusion, ascites, arrhythmia and mortality.

Ebstein anomaly is characterized by downward displacement of the septal and posterior leaflets of the tricuspid valve which are attached to the right ventricular septum. The anterior leaflet is elongated and is displaced downward within the right ventricular cavity causing "atrialization of the right ventricle" (i.e., the right ventricle is small). There is usually a PFO or an ASD or PS (pulmonic stenosis). Cyanosis depends up on the right to left shunt. Auscultation may reveal a triple or quadruple gallop rhythm and a split second heart sound. A pansystolic murmur of tricuspid insufficiency or an ejection murmur of PS may be heard. The electrocardiogram shows a right bundle branch block pattern, giant P waves and sometimes first degree AV block or WPW syndrome (delta wave). Chest x-ray shows a huge right atrium and gross cardiomegaly. Echocardiography reveals the lesions of Ebstein anomaly and only rarely is cardiac catheterization needed. Treatment is mainly palliative and there are no good surgical options. In older patients, tricuspid annuloplasty and rarely tricuspid valve replacement may be performed. Prognosis depends on the severity of the lesion. Prognosis is good with mild lesions and poor with severe lesions with other associated anomalies/malformations.

Hypoplastic left heart syndrome consists of a combination of mitral stenosis or atresia, severe aortic stenosis or atresia, and a small left ventricle. Systemic circulation depends on the patency of the ductus. These infants may appear reasonably well at birth until either the pulmonary vascular resistance drops or the PDA closes. They then present with shock, variable cyanosis, poor pulses, poor perfusion and

CHF. A systolic murmur may or may not be present. Chest x-ray shows increase vascularity and EKG may show RV hypertrophy. Echocardiography is diagnostic. Early management consists of administration of PGE1 and treatment of CHF. Surgery consists the Norwood surgical procedure and a few centers perform cardiac transplantation for this lesion. Prognosis is guarded.

Questions

1. A two day old cyanotic infant with a grade 3/6 ejection systolic murmur is noted to have decreased pulmonary vascular markings on chest x-ray and left axis deviation on EKG. The most likely diagnosis is:
   a. Tetralogy of Fallot
   b. Transposition of Great Vessels
   c. Truncus Arteriosus
   d. Tricuspid Atresia

2. A 2 year old infant is noted to have mild cyanosis who assumes a squatting position during long walking. He is noted to have increasing fussiness followed by increasing cyanosis, limpness and unresponsiveness. The most likely underlying lesion is:
   a. Hypoplastic left heart
   b. Transposition of the Great Vessels
   c. Anomalous Pulmonary Venous Return
   d. Tetralogy of Fallot
   e. Aspiration with obstruction to air passages

3. An infant with a marked cyanotic congenital heart defect with decreased pulmonary vascularity should be treated with:
   a. Digoxin
   b. Indomethacin
   c. Prostaglandin E1
   d. Epinephrine

4. Cyanosis is produced by the presence of deoxygenated hemoglobin of at least:
   a. 1-2 gm/dL
   b. 3-5 gm/dL
   c. 6-8 gm/dL
   d. 9-10 gm/dL

5. A "tet spell" or "blue" spell of tetralogy of Fallot is treated with all of the following except:
   a. oxygen
   b. knee chest position
   c. morphine
   d. digoxin
   e. propranolol
   f. phenylephrine
   g. sodium bicarbonate

6. Pulmonary vascularity is increased in all of the following except:
   a. TAPVR
   b. Tricuspid atresia
   c. TGV
   d. Hypoplastic left heart

7. Pulmonary vascularity is decreased in all of the following except:
   a. Tetralogy of Fallot
   b. Pulmonary atresia
   c. TAPVR
   d. Tricuspid atresia

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Answers to questions
1.d, 2.d, 3.c, 4.b, 5.d, 6.b, 7.c

Chapter VII.4. Rheumatic Fever
David K. Kurahara, MD

An 11 year old Polynesian male presents with fever up to 39 degrees (102 degrees F), joint pain and swelling, along with shortness of breath. The fever comes and goes at random times of the day. The symptoms have been present now for 4 days. Two days ago, his right knee was painful and swollen, but today it has improved. The joints involved today include the right ankle and left knee. They are quite tender, painful and also swollen. The shortness of breath occurs with walking, but he is now unable to walk because of the joint pain. He also has some shortness of breath with lying down flat when he is trying to sleep.

Exam: VS T 38.2, P 160, RR 32, BP 100/60, oxygen saturation 94% in room air. He is tired appearing with tachypnea and tachycardia. HEENT: Enlarged, erythematosus tonsils with exudates. Lungs are clear but with tachypnea. Heart sounds are tachycardic with a holosystolic murmur 3/6 heard at apex with radiation to axilla. No gallops are heard. His PMI is prominent (size of silver dollar) at the 7th intercostal space in the mid-axillary line. His abdomen is soft with normoactive bowel sounds. His liver edge is 6 to 7 cm below the RCM. His left knee is swollen and extremely tender with warmth. He has difficulty with range of motion but can flex his knee 30 degrees passively. His right ankle is very swollen and warm. He has limited subtalar motion. Both his knee and ankle are very tender even to touch. Neuro: No abnormal movements of arms, hands, or tongue are noted. He is unable to walk due to pain.

Clinical course: The child is admitted to the hospital. Initial laboratory work includes a erythrocyte sedimentation rate of 110, a CRP of 9.5, and a chest X-ray with cardiomegaly present. EKG reveals a prolonged PR interval. ASO titer is 754 and streptozyme is 1:600. The diagnosis of acute rheumatic fever (ARF) is made and he is initially started on salicylate therapy at 75 mg/kg/day, and his arthritis improves dramatically. However, the next day an echocardiogram confirms severe mitral insufficiency. Due to the significant cardiac disease with elements of congestive heart failure he is switched to corticosteroids and improves. His heart size decreases over the next 2 weeks, and when it normalizes he is switched back to salicylates for a total treatment duration of 8 weeks. He does have a persistent murmur after this time however. He is started on intramuscular benzathine penicillin, which is given every 4 weeks for streptococcal prophylaxis.

The terms of Acute Rheumatic Fever and Rheumatic Heart Disease are sometimes confused. Proper use of these terms requires some knowledge of the disease entities even though their pathogenesis and relation to streptococcal infection is nearly identical. ARF is usually used to describe the initial or acute onset of the disease. In our case, this being the first initial presentation of the disease, it would be correct to call this ARF. The case fulfills modified Jones criteria as will be discussed below. However, as time goes on it is found that this child has a persistence of the murmur. He also had severe carditis which caused his acute congestive heart failure, as manifestations of ARF, but he subsequently develops chronic heart disease as a sequelae of the ARF carditis and thus it would also be correct to describe him in terms of a more chronic form of the disease, namely Rheumatic Heart disease (RHD). This term implies there has been significant valvulitis, enough to cause valvular scarring. This child is at an increased risk of requiring a valve replacement in the future, especially if he develops another episode of the disease, which puts great emphasis on him receiving long term penicillin prophylaxis, to prevent him from getting streptococcal disease and possible reoccurrence of ARF with worsening RHD.

The study of ARF and RHD parallels the history of modern medicine. At one time in the early 1900s children filled the beds of hospitals dedicated to treat only rheumatic fever. The treatment at that time was simply bed rest, sometimes for up to a year. With improvements in living conditions, reduction of crowding, and industrialization, ARF incidence has steadily decreased in the United States (1). When the link to streptococcal infection was found, the usefulness of using penicillin to prevent future attacks was also established, and ARF incidence decreased further.

However, certain areas of the country and large parts of the under-developed world, including India, Sub-Saharan Africa, Turkey, Australia, New Zealand, and Tonga, still experience many cases of ARF (2). In the United States, there remains a high incidence of ARF in Hawaii and Utah (3-6). In Hawaii, the ethnic groups at greatest risk are those of Polynesian heritage, with Samoan children being at greatest risk (4-6). The Samoan children also appear to be at greater risk of developing carditis (4,5). More than 75% of patients with ARF, in Hawaii, have Polynesian ethnicity within their heritage.

To accurately diagnosis ARF, one should adhere to the modified Jones criteria (7). These criteria have been modified over the years since it was first developed by T. Duckett Jones. The last modification removed the minor criteria of "a history of ARF", since there are fewer cases seen on the continental United States, and the authors wanted to concentrate on first time cases, rather than recurrent ones (8). These criteria were developed to accurately diagnose ARF. It is very important to use these criteria when making the diagnosis. If the criteria are not used, and the patient is misdiagnosed, you may be subjecting the patient to needless penicillin injections for years. It is sometimes difficult for ARF patients to get life insurance and medical insurance later, due to the implications of the cardiac disease. Therefore, the diagnosis must fulfill the modified Jones criteria.

The modified Jones criteria are categorized into Major and Minor criteria. These criteria are based on how specific the manifestation is to the diagnosis of ARF. In other words, a Major criterion is much more specific to ARF than the Minor criteria. Therefore, if a child that has two Major criteria, they can fulfill Jones criteria for the diagnosis, as long as they have some evidence of streptococcal disease. On the other hand, if there is evidence of only one Major criterion, they need two minor criteria to fulfill the diagnosis, along with evidence of streptococcal infection. Since the minor criteria are less specific for the diagnosis of ARF, you cannot make the diagnosis of ARF with just minor criteria. The symptoms may be dampened by giving aspirin or other non-steroidal anti-inflammatory medications too early, thus not allowing the manifestations to fully develop.

Modified Jones Criteria (two majors or one major + two minors required) (7)

Major criteria: carditis, migrating polyarthritis, chorea, erythema marginatum, subcutaneous nodules.

Minor criteria: fever, arthralgia, elevated acute phase reactant (CRP or ESR), prolonged PR interval (i.e., first degree AV block). Leukocytosis used to be a minor criterion, but it no longer is.

Plus: All must have evidence of streptococcal infection (positive ASO titer, Streptozyme, positive streptococcal throat culture.

The polyarthritis must be migratory. This manifestation is one of the most common of the major criteria in ARF. Usually one joint becomes involved and over a few days resolves, then another joint(s) becomes involved as demonstrated in our case. Occasionally, the first joint does not resolve completely by the time the second joint becomes involved, and this is termed "additive arthritis", and also fulfills a diagnosis of migrating polyarthritis. In ARF, two or more joints are considered polyarthritis. If migrating polyarthritis is present

you cannot use the minor criteria of "arthralgias", as virtually all the children with polyarthritis from ARF have a significant amount of pain. The most common joints involved are large joints, usually those that weight bear. Knees and ankles are most often involved, although elbows and wrists can also be involved. Metatarsophalangeal joints can be involved and one can screen for their involvement by squeezing them together, across the foot, and eliciting pain. The joint pain of ARF is typically very severe even if the visual findings are not very impressive. Merely touching the joint often elicits severe pain. Lower extremity joint involvement renders these patients non-ambulatory.

The presence of a new murmur due to cardiac disease (i.e., carditis) is always sought on physical exam of a child that presents like our case. A very careful cardiac examination should include a description of the PMI and its location (for evidence of congestive heart failure). Our case had an enlarged PMI that was displaced to the lateral side indicating cardiomegaly. The enlarged liver size gave further evidence of congestive heart failure. These findings are important to note, especially in a child with possible symptoms of orthopnea. Congestive heart failure is a severe form of carditis in ARF, and is managed more aggressively, often needing corticosteroids, diuretics, digoxin, and occasionally inotropic agents.

More often, the carditis of ARF is not quite this severe, but can be problematic. The most common valve involved is the mitral valve. The second most common valve involved is the aortic valve. Classic mitral insufficiency sounds like a holosystolic murmur heard at the apex which radiates to the axilla. There are very few cardiac lesions that can be heard in the axilla. Besides mitral insufficiency, a ventricular septic defect could be heard in the axilla, but this murmur is usually heard all over the precordium. The murmur of aortic insufficiency is a diastolic murmur (difficult to hear) that is usually heard best at the upper left sternal border. There is often a decrescendo component to this murmur that is sometimes very high pitched. One should also listen for a rub which would indicate pericarditis and a gallop for evidence of congestive heart failure.

The initial valvulitis of ARF results in valvular insufficiency. Subsequently as RHD develops, if enough inflammation has occurred on the valve leaflets of the mitral valve, the leaflets may scar and become adherent to each other, resulting in mitral stenosis (usually seen late in the patient's course, sometimes after repeated episodes of ARF). The murmur of mitral stenosis is a diastolic murmur, although it is described as occurring in mid-diastole, rather then later in diastole like aortic insufficiency. Similarly, aortic stenosis may subsequently result from initial aortic insufficiency.

The other major criteria describe manifestations that are less often seen in ARF. These manifestations are usually seen in less than 20% of cases. Chorea is the more common of these three, and is often difficult to diagnosis. It is also known as Sydenham's chorea or St. Vitus dance, and causes purposeless and involuntary movements. The hands and tongue are often involved. Parents may also notice the child having mood swings or just "not acting right". Emotional lability is often seen with this manifestation of chorea. Occasionally, chorea occurs so late in the illness that the laboratory tests including ASO titers, ESR, and CRP titers may all be normal. Thus, chorea is often termed a "subacute" phenomenon of rheumatic fever (as opposed to acute rheumatic fever). Despite this lack of evidence of inflammation these patients can develop cardiac disease. Typically, the chorea is not present while sleeping. The chorea usually resolves with time.

Both subcutaneous nodules and erythema marginatum are less common in ARF, but if they are seen there, there is a greater chance of the patient developing carditis. The nodules are usually small being <0.5 cm in diameter, and are seen in <20% of patients with ARF. They are located over areas that tend to be more prominent and rub against surfaces causing microtrauma. For example, they can be located at the tips of the elbows, around the joints, and the bony prominences of the spinal column. It is worthwhile spending some time looking for the nodules as their presence heralds severe carditis (9).

Erythema marginatum is the most rare of the major signs/criteria seen in ARF. It occurs in 5 to 10% of cases. It is a rash usually present over the trunk, and almost never seen over the face. The erythema is described as an evanescent pink eruption with irregular but well-demarcated borders (9). Individual lesions usually last for hours and then disappear, which is why it seen so infrequently. If this rash is found, careful cardiac exams should be done, as these children are at greater risk to develop carditis.

When evaluating a child with acute onset arthritis, the differential diagnosis can be quite overwhelming. Certain elements of the history and physical can help lead to the correct diagnosis. In ARF, the modified Jones criteria are very helpful, but there are other findings which can also help confirm your suspicion of ARF. For example, you should be able to describe the type of arthritis you are observing. Are the joints swollen and without much tenderness, but very stiff in the morning like is seen in Juvenile Rheumatoid Arthritis? Are the effusions rather bland and non-tender lasting for a few days as they are in Systemic Lupus Erythematosus? Is the joint so tender and swollen it can not be moved even a few degrees as is seen in a septic joint? In ARF the joints are usually somewhere between these extremes of pain/tenderness. They can be very painful, but yet if you do not move them, the child is still fairly comfortable. In a septic joint, the child usually has pain even at rest. The classic ARF joint is very warm, only sometimes erythematosus, and very tender. Even the weight of the bed-sheet can cause pain, and this finding is sometimes called the "bed-sheet sign". The tenderness is almost hyper-esthetic, with light pressure causing pain.

The treatment of ARF and RHD is often confusing for the medical students and housestaff. If it is confusing to such well trained individuals, just think of the frustration parents may feel when trying to understand the treatment regiment. To simplify the treatment we will separate the regimen into acute management of the inflammatory condition of ARF, and prevention of further episodes of ARF or antibiotic prophylaxis. With any good treatment plan a "healthy" amount of translating medical jargon into simple terms for the parents is needed, which will help compliance issues. This is especially important when dealing with a long term treatment like benzathine penicillin injections on a monthly basis.

The acute arthritis of ARF will normally respond very dramatically to high dose salicylate therapy. The aspirin dose is 70-100 mg/kg/day divided into QID dosing with a maximum dose of 975 mg QID. Aspirin tablets come in 81 mg, 325 mg, and 975 mg. Use enteric coated tablets if available, and ask patients to eat prior to taking the aspirin. Monitor salicylate levels and liver function tests while on aspirin. Be very careful with ARF patients who have some elevation in liver function tests prior to being put on aspirin, since a low grade inflammatory hepatitis can be seen in ARF. The aspirin could aggravate this problem. The treatment duration is usually 4 to 6 weeks or until the ESR or CRP returns to normal. If it is stopped too early, the arthritis usually returns.

If the carditis is mild and the child is asymptomatic from a cardiovascular standpoint, then salicylate therapy is usually given. However, if there is evidence of severe carditis, then corticosteroids are indicated. Severe carditis is manifested by evidence of congestive heart failure (e.g., gallop rhythm, cardiomegaly, etc.) or severe myocardial disease (e.g., two valve disease or a new or a worsening arrhythmia). Close follow-up and evaluation by the cardiology service is warranted. Repeat echocardiograms will be needed. Corticosteroids are indicated for severe carditis under the direction of a cardiologist. Prednisone is usually given for 2 to 3 weeks followed by aspirin while the corticosteroids are tapered.

Some RHD patients will develop an indolent flare-up of their cardiac disease which is far removed in time from their first episode of ARF. These patients are extremely challenging. During this indolent flare-up, they develop no fever or arthritis, but just present with worsening cardiac disease. Sometimes, this is found on repeat echocardiograms, or by symptomatic CHF returning without other warning signs of a reoccurrence of rheumatic fever. Often an increase in the ESR, CRP, and ASO titer is also seen, indicating a sub-clinical case of streptococcal infection leading to the recurrence of the immune reaction in ARF. These patients may respond to another course of corticosteroids. This underscores the importance of close follow up by the cardiology service.

Antibiotic prophylaxis against streptococcal infections is utilized to prevent a recurrence of ARF, and thus prevent further damage to the valves. Long term prophylaxis needs to be carefully described to the parent and child. Many of the families do not understand why the child needs penicillin injections when he or she feels fine, following the episode of ARF. Many mistakenly think the injections are for the arthritis and therefore do not comply with this regiment once the arthritis has resolved.

There is currently some debate about whether the penicillin injections should be given every 3 or 4 weeks, as well as, the length of treatment (10), but these arguments are beyond the scope of this article. Suffice it to say, these children require the prophylaxis as long as they are at greatest risk of contracting streptococcal infection, which means at least until adulthood, and some require it for their lifetime. We have recommended that our patients receive it every 4 weeks, partly due to compliance concerns. With every 3 weeks it is difficult for families to remember when to get their injection, and this has an increased negative effect on compliance.

Oral antibiotics can also be used but have higher recurrence rates of ARF, than the intramuscular injections. If the child forgets one or two days of oral antibiotics, they are at risk of contracting streptococcal infection, and this is the reason for the higher recurrence rates with oral antibiotics. In penicillin allergic patients, the only option is to utilize oral antibiotics.

It is important to counsel families on the importance of preventing subacute bacterial endocarditis (SBE) from occurring in RHD patients. Like children with other cardiac malformations, once a child is diagnosed with RHD, they are at similar risk of developing SBE. Antibiotics for prophylaxis against alpha-hemolytic viridans streptococci valvular infection is important prior to and following any dental or gastrointestinal procedure. These recommendations can be found elsewhere in this textbook.

The development of persistent cardiac disease is dependent on the amount of inflammation suffered by the cardiac structures during the acute period of disease and by the number of recurrences. Each recurrence will cause increased damage to valvular components and an increased likelihood of mitral stenosis, and the need for valve replacement. The mortality from ARF and RHD probably lies somewhere between 1 to 5 %, although most of the prognostic studies were done decades ago. A classic study demonstrated that with increased carditis severity, there is an increased risk of subsequent cardiac disease (see below).

Estimated occurrence of Rheumatic Heart Disease 5 years after ARF (11,12)
Initial clinical status (%risk of subsequent cardiac disease)

No carditis (4%)
Soft apical murmur (18%)
Loud apical murmur (32%)
Diastolic murmur (47%)
CHF or pericarditis (100%)

Few prognostic studies have been done in the recent past, and should probably be repeated to understand the current risk to children with ARF developing chronic cardiac disease and RHD.

The diagnosis of ARF can be challenging and difficult to make. However, the modified Jones criteria can be extremely helpful in assisting the clinician in this process. It is important to verify the development of the major criteria before starting treatment, because treating too early may stop migration of the arthritis and make fulfilling Jones criteria more difficult. Without fulfilling Jones criteria it is difficult to justify long term penicillin prophylaxis, which may last decades, to patients and their families.

Questions (authored by Neal Rojas, MD-UCSF Residency Program)

1. What is the main difference between Rheumatic Heart Disease (RHD) and Acute Rheumatic Fever (ARF)?
    a. In ARF there is an elevated ESR
    b. In RHD there is a prolonged P-R interval
    c. In ARF there is a history of arthralgias
    d. In RHD there is evidence of chronic heart disease
    e. In ARF there is evidence of erythema marginatum

2. All of the following are included in the revised Jones Major criteria EXCEPT:
    a. New murmur (carditis)
    b. Migrating polyarthritis
    c. Chorea
    d. Maculopapular rash
    e. Subcutaneous nodules

3. A 7 year old girl presents with a tender and swollen right knee as well as a more recently appearing swollen left wrist. She also has a fever. This patient fulfills which of the following modified Jones criteria?
    a. 1 Major 1 minor
    b. 1 Major 2 minors
    c. 2 Majors
    d. 2 Minors
    e. 1 Major only

4. Which of the following symptom lists of ARF are in the correct order of most common' least common?
    a. Erythema marginatum, subcutaneous nodules, carditis, fever
    b. Arthritis, carditis, chorea, erythema marginatum
    c. Chorea, erythema marginatum, subcutaneous nodules, carditis, fever
    d. Arthritis, chorea, fever, carditis, subcutaneous nodules
    e. Fever, chorea, carditis, erythema marginatum

5. Salicylates are directed primarily at what symptom in ARF?
    a. Rash
    b. Fever
    c. Arthritis
    d. Chorea
    e. Carditis

6. Corticosteroids are directed primarily at what symptom in ARF?
    a. Rash
    b. Fever
    c. Arthritis
    d. Chorea
    e. Severe Carditis

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Answers to questions

1.d, 2.d, 3.a, 4.b, 5.c, 6.e

Chapter VII.5. Carditis
David K.M. Wong, MD

This is a 12 year old boy with a 2 day history of fever, nausea, vomiting, anorexia, chills, and night sweats. During the last 24 hours, his symptoms not only worsened, but he started complaining of shortness of breath. At this time, he is brought to the Emergency Department. His past medical history is only remarkable for a small ventricular septal defect which has never bothered him before. He denies any surgical history or past hospitalizations. Family history and social history are noncontributory.

Exam: VS T 38.5, pulse 140, BP 90/45, RR 40, oxygen saturation 92% on room air. Weight and height are at the 50th %ile. He is alert, subdued and somewhat toxic in appearance. Eyes are clear (no conjunctival hemorrhages). ENT exam is normal. His neck is supple without adenopathy. Lung exam reveals tachypnea and coarse bibasilar breath sounds, but no dullness to percussion or pleuritic chest pain. Cardiac exam reveals tachycardia, and a loud, harsh, blowing, grade 3/6, holosystolic murmur, heard best over the lower left sternal border, but no frictional rubs and no gallops. His abdominal exam is normal. No rashes or ecchymoses are noted. No neurological abnormalities are noted.

Chest x-ray identifies multiple delicate nodular opacities bilaterally. A CBC shows a WBC 25,500, with 22% bands, 63% segs, 10% lymphs, and 5% monos. Hgb 14.5, Hct 44%, platelet count 300,000. ESR is elevated at 92. Chemistry panel is within normal limits. Urinalysis reveals microscopic hematuria. Two blood cultures, each more than 12 hours apart, are still pending. EKG reveals a sinus tachycardia. An echocardiogram reveals a small VSD with minimal left-to-right shunt, but no vegetations or pericardial effusion. Ventricular and valvular function are normal.

Clinical course: He is admitted to the hospital for possible endocarditis. IV antibiotics (vancomycin and gentamicin) are started. A CT of the chest reveals evidence of septic emboli in both lungs. On the second hospital day, both blood cultures grow out Staph aureus. On hospital day 3, the Staph aureus is methicillin/oxacillin sensitive, so his antibiotics are changed to oxacillin. On hospital day 8, his temperature returns to normal and by the 6th week of IV antibiotic therapy, his subsequent blood cultures are negative and he is discharged home.

Carditis (inflammatory conditions of the heart) includes myocarditis, pericarditis and endocarditis. Endocarditis includes valvular inflammation (often called valvulitis). Aortitis is sometimes included in carditis. Endocarditis may be infectious or due to rheumatic fever. Pericarditis and myocarditis are usually viral or post-viral, but they may be due to rheumatic fever as well. Autoimmune conditions may also cause carditis. Rheumatic fever and autoimmune conditions are covered in separate respective chapters.

Infective Endocarditis

Prior to the era of antibiotics, patients suffering from infective endocarditis had mortality rates of nearly 100%. However, with the introduction of antibiotics, the present day mortality rate for this disease in the pediatric population ranges between 20-30%. The present trend for this disease has the average pediatric age of onset increasing from 5 to 12 years old. Some hypothesize the reason for this is due to the current increase in survival rate of children with congenital heart disease.

It is theorized that the cause of infective endocarditis stems from the hemodynamically turbulent flow which causes endothelial thickening that provides a place for a platelet and fibrin thrombus to develop. This site becomes the nidus of bacterial growth for susceptible adhesive microorganisms. Therefore, conditions which predispose turbulent blood flow in the heart are risk factors for infective endocarditis. Such conditions include ventricular septal defects (VSD), patent ductus arteriosus (PDA), aortic valvular disease, atrioventricular septal defect (AVSD, also known as endocardial cushion defect or AV canal), prosthetic valves, tetralogy of Fallot, and chronic rheumatic heart disease. In underdeveloped countries where rheumatic heart disease is common, it is the most common cause for infective endocarditis. However, congenital heart disease is the most common risk factor in pediatric practices of the United States. The mitral valve is the most commonly affected, followed by the aortic valve, then the tricuspid valve. Other risk factors include situations which increase the risk of bacteremia, such as: IV drug use (which predisposes infective endocarditis to the right side of the heart), indwelling IV catheters, intraarterial catheters, severe burns, dental procedures, or recent cardiac surgery.

It is estimated that 80% of all pediatric infective endocarditis are due to alpha-hemolytic streptococci and S. aureus. Alpha-hemolytic streptococci (which includes strep viridans) are responsible for 75% of subacute endocarditis and S. aureus is responsible for 50-70% of acute endocarditis.

The clinical course of infective endocarditis varies from an acute to subacute course and is usually based on the offending microorganism. Traditionally, the microorganisms which are responsible for acute infective endocarditis include Staphylococcus aureus, Streptococcus pyogenes, or Neisseria gonorrhoeae. Microorganisms usually responsible for subacute infective endocarditis are the less virulent Streptococcus viridans (alpha strep). These distinctions, though useful clinically, do not always hold. Therefore, S. aureus may cause a subacute course, and S. viridans may be responsible for an acute endocarditis. In the pediatric setting, the clinical distinctions are still useful, perhaps more so than in the elderly population.

Acute infective endocarditis is characterized by a rapidly progressive clinical picture of sepsis, high fever, headaches, nausea, vomiting, diarrhea, cough, shortness of breath, and early cardiac decompensation. On the other hand, the subacute course is characterized as an insidious, flu-like syndrome, associated with malaise, anorexia, +/- fever. In the pediatric population, it is rare to find splinter hemorrhages, Osler nodes (painful, red, nodular lesions most commonly found on fingers), Janeway lesions (small, erythematous, nontender areas of the palms and soles), and Roth spots (retinal hemorrhages with central clearing). If the course is prolonged, then splenomegaly, weight loss, night sweats, anemia, or petechiae may develop. In 20% of infective endocarditis, a new cardiac murmur or change in a preexisting murmur occurs. A subacute course of infection is unusual under the age of 2 years old. Most patients with endocarditis younger than 2 will have an acute fulminating disease.

Embolic episodes may also be a part of the clinical course, however this is more common in adults than in children. Emboli originating from left-sided endocarditis may cause renal infarcts resulting in frank hematuria, splenic infarcts resulting in left flank pain, or stroke-like symptoms resulting from cerebral emboli. Emboli from right-sided endocarditis may cause chest pain and shortness of breath due to pulmonary embolism.

Several sources describe a diagnostic criteria (the Duke criteria) to allow early recognition of endocarditis, when vegetations are still too early to detect. A patient is considered to have infective endocarditis if 2 major criteria or 1 major plus 3 minor criteria are met. The major criteria are: positive blood cultures x2 and endocardial abnormalities on echocardiography. The minor criteria are: presence of a

predisposing condition (i.e., valve abnormality), fever greater than 38 degrees C, embolic episode (i.e., splenic infarct), and immunologic phenomena (i.e., Osler nodes).

Blood cultures are the most valuable laboratory tests in making the diagnosis of infective endocarditis. Controversy lingers as to the exact number of cultures that should be obtained for each patient with suspected infective endocarditis. However, the collection of 2 to 3 blood cultures over a 24 hour period will suffice in most cases. Approximately 5% of patients with endocarditis will have negative blood cultures. In some cases, the microorganism contained in the vegetation are unexposed, encased in fibrin and platelets. Antibiotic therapy prior to obtaining blood cultures will reduce the likelihood of recovering the organism in the blood. Therefore, it is very important to obtain blood cultures prior to antibiotic treatment. Fungi or candida can cause endocarditis rarely, but these will eventually grow out of most blood cultures (though very slowly).

Other laboratory tests are not as helpful in making the diagnosis of infective endocarditis, but they may be helpful in monitoring clinical progress. Elevated erythrocyte sedimentation rate (ESR) is commonly found in both acute and subacute endocarditis. During antibiotic therapy, a decrease of the ESR signifies that the treatment is most likely effective. Like many other infectious diseases, a leukocytosis with an accompanying left shift may be seen, although this is more common in the acute setting than the subacute course. Microscopic or macroscopic hematuria is also a common laboratory finding. Microscopic hematuria is most likely due to immune complex depositions in the glomeruli, whereas macroscopic hematuria is most likely a result from renal embolization. If the course is chronic, such as in the subacute cases, normocytic/microcytic anemia may occur.

The most helpful diagnostic procedure is echocardiography. Echocardiography is most helpful in children with normal cardiac anatomy or with isolated valvular abnormalities. However, this procedure is not 100% sensitive or specific, therefore a negative echocardiogram does not rule out endocarditis. Recently, transesophageal echocardiography (TEE) has had better results than the transthoracic approach in adults. Although, TEE is currently used intraoperatively in children, the usefulness for this procedure in children with endocarditis remains uncertain.

The differential diagnosis for infective endocarditis is complex since this disease has variable clinical presentations. Because infective endocarditis commonly presents with fever, arthralgias, and a positive rheumatoid factor; juvenile rheumatoid arthritis, Kawasaki's disease, rheumatic fever and other connective tissue disorders should be considered in the differential diagnosis. Neurologic manifestations from infective endocarditis may also mimic that of meningitis, cerebritis, or toxic encephalopathy. If hematuria is present, one must also consider other renal diseases. If S. aureus bacteremia along with an increasing ESR is present in a patient with infective endocarditis, one must consider osteomyelitis or septic arthritis. Cardiac myxomas or rheumatic carditis must also be considered if a patient presents with a new or changing heart murmur. The diagnosis of infective endocarditis should be considered in any child with persistent unexplained fevers especially if they are considered at high risk such as history of congenital heart defects or IV drug use.

Isolation of the infecting microorganism by blood culture is extremely important, not only in making the diagnosis, but also in planning for treatment. The microorganisms that are revealed from the blood cultures will strongly determine the type of antibiotic regimen to be used. The physician must be guided by the antibiotic susceptibility pattern. Although antibiotic regimens vary depending on the infective microorganism, one general principle is true in the treatment of infective endocarditis: complete eradication of the infecting microorganism with bactericidal agents will usually require weeks of therapy. For example, patients with blood cultures that grow out Streptococci will require 4 weeks of penicillin G and patients with Staph. aureus will require 6 weeks of oxacillin (if they are methicillin/oxacillin sensitive). Initially when blood cultures are still pending, empiric antibiotics should be started. Empiric therapy includes coverage for the common, Streptococci and S. aureus, but also for the less common MRSA (methicillin resistant Staph aureus) and Gram negatives, therefore vancomycin and gentamicin are the preferred regimen.

Determination of MIC and MBC levels for the causative bacteria will assist in determining the potential for outpatient treatment with oral antibiotics (refer to the chapter on MIC and MBC levels).

Obtaining occasional blood cultures during the first 8 weeks after cessation of treatment is warranted, because most relapses occur during this period. There are several common indications for surgery. These include a significant embolic event, persistent infection, and progressive congestive heart failure especially when the aortic or mitral valve is involved.

Prophylactic antibiotics are recommended for children who are at risk to develop infective endocarditis, while undergoing procedures that may induce a bacteremia. At risk patients include those who have significant heart defects associated with turbulent blood flow (e.g., VSD, mitral valve prolapse, etc.), prosthetic conduits, or prosthetic heart valves. The recommended antibiotic regimens for prophylaxis include amoxicillin 50mg/kg PO 1 hour before the procedure or ampicillin 50mg/kg IM or IV within 30 minutes of the procedure. If the patient is allergic to penicillin, an alternate drug may include clindamycin 20 mg/kg PO 1 hour before procedure or cefazolin 25mg/kg IM or IV within 30 minutes of the procedure. In general, any dental or surgical procedure involving the respiratory, gastrointestinal, or genitourinary tract that induces bleeding from the gingival or mucosal surface, can predispose at risk patients to bacteremia. Therefore, antibiotic prophylaxis should be considered in these situations. The maintenance of optimal dental care and oral hygiene is also important for children at risk for infective endocarditis.

At present, the mortality rate is between 20 and 30%. Mortality rates are slightly higher in patients with acute staphylococcal infection, fungal infection, and prosthetic valve endocarditis. Mortality may be caused by sudden perforation of the aortic valve with severe aortic insufficiency, chordal rupture with resultant mitral insufficiency, myocardial infarction, or intramyocardial abscess formation with the development of a myocarditis.

Myocarditis

Myocarditis is defined as an inflammatory response within the myocardium. The categories of myocarditis are divided into infectious myocarditis and generalized autoimmune myocarditis. In either case, the histological features of the myocardium reveal myocardial necrosis with accompanying inflammatory reactions.

The most common cause of pediatric infectious myocarditis in the western world is viral in nature. Any virus may cause this, but the most notable viruses are coxsackie viruses, echovirus, influenza virus, mumps, and rubella. Non-viral infectious myocarditis may include protozoan infections, Lyme disease, hemolytic uremic syndrome or complications from tuberculosis. Whatever the suspecting etiological may be, the pathophysiology remains unknown. Some speculate infectious myocarditis may result from toxins secondary to the infectious agent, others speculate the mechanism is secondary to an immune reaction.

The clinical manifestations of this disease, varies from the more common subacute course to the severe course which manifests as heart failure that may be accompanied by arrhythmias. There is no single characteristic profile for infectious myocarditis. A nonspecific systemic viral infection is usually followed by a latent period. The latent period is followed by variable nonspecific signs and symptoms such as fever, diarrhea, anorexia, pallor, mild jaundice, or lethargy. Diminished heart tones may be the only clinical clue pointing toward

myocarditis. If the disease progresses, cardiac enlargement may ensue, along with a nonspecific cardiac arrhythmia. The end result may eventually lead to symptoms of heart failure, such as tachypnea, dyspnea, and fatigue.

Much like the clinical manifestations, results from laboratory and investigational tests are often variable. Erythrocyte sedimentation rate, white blood cell count, and cardiac enzymes tend to vary from elevated to normal, depending on the severity of the disease. Chest radiographs may show an enlarged heart and depending on the severity of the heart failure, pulmonary venous congestion may be present. Electrocardiographic (EKG) abnormalities are common, but only nonspecific findings are present in infectious myocarditis. Often, a sinus tachycardia is present, with lowering of the QRS complexes in the standard leads and/or precordial leads. The T-waves may be flattened or inverted with changes in the ST segment. Echocardiography may reveal a nonspecific dilation of the heart chambers, most commonly the left ventricle. The left atrium may be enlarged if mitral insufficiency is present. The main importance of an echocardiogram is to exclude a pericardial effusion and to assess myocardial contractility. In addition to the echocardiogram, radionuclide angiography has been used to perform serial measurements of the left ventricular function. Controversy remains on routine endomyocardial biopsies for suspected myocarditis because the pathology is often patchy, therefore a negative biopsy cannot exclude the diagnosis. Essentially, the diagnosis of infectious myocarditis is a diagnosis of exclusion.

The treatment of myocarditis most often focuses on the treatment of arrhythmias and congestive heart failure. If an infectious agent is identified, then the appropriate therapy should be instituted, however in most cases no infectious agent will be found. Treatment of the heart failure consists of bedrest, oxygen, and congestive heart failure treatment (e.g., inotropes, diuretics and ACE inhibitors). Digoxin is controversial since this drug may induce ventricular arrhythmias. Other controversial and unproven treatment therapies include drugs that decrease the inflammatory response such as corticosteroids, immunosuppressive agents, and high-dose IV immunoglobulins.

The prognosis of the subacute course of myocarditis is good. Most patients will recover in several weeks to months with the heart size reverting back to normal within a year. However, in cases where heart failure recurs, the prognosis is poor.

Generalized autoimmune myocarditis is often one aspect of a syndrome secondary to a collagen or connective tissue disease. Autoimmune myocarditis is found infrequently in children. The more common cardiac finding in SLE is pericarditis.

Pericarditis

Pericarditis is defined as an inflammatory reaction of the pericardium. Etiologies include acute bacterial pericarditis, acute viral pericarditis, postpericardiotomy syndrome, acute rheumatic fever and uremia. Echocardiography is the most important diagnostic test, which will reveal the presence of a pericardial effusion surrounding the heart. Moderate pericardial effusion secondary to pericarditis may also show up on x-ray as an enlarged cardiac silhouette but the x-ray will not be able to distinguish pericardial effusion from myocardial dilation. In borderline cases, comparisons of previous x-rays may prove helpful. Electrocardiography (EKG) may be useful in the initial stage of the disease, when ST segments are elevated in all leads except V1 and aVR. After a few hours to days, the ST segments may return to baseline, and the T waves become flat. A low voltage (low amplitude) EKG may be seen if the pericardial effusion is large enough.

Much like infective endocarditis, the incidence of acute bacterial pericarditis has dramatically declined since the development of antibiotics. The most common settings for acute bacterial pericarditis include septicemia or hematogenous or direct spread into the pericardium from another site, such as with pyelonephritis, osteomyelitis, tonsillitis, bacterial pneumonia and empyema. The common microorganisms responsible for most acute bacterial pericarditis are Haemophilus influenzae type B, Staphylococcus aureus, pneumococcus, meningococcus, streptococcus species and tuberculosis infection. Patients with acute bacterial pericarditis will usually manifest with acute onset of chest pain, high fever, tachycardia, frictional rub, tachypnea and toxemia. Acute bacterial pericarditis often is associated with an infection elsewhere, therefore an intensive search for the primary source is essential. Blood cultures are important and it is recommended that three to five sets should be obtained in the first 1 or 2 days after admission. These blood cultures are positive 40-80% of the time and the appropriate antimicrobial agent given for 4 to 6 weeks should be chosen based on the susceptibility testing. Acid-fast stains for tuberculosis of the sputum, gastric contents, or urine are considered if blood cultures come back negative.

Acute viral pericarditis is often associated with the aforementioned viral myocarditis. And like the viral myocarditis, the most common viral agents responsible for viral pericarditis include group B coxsackie virus, echovirus, adenovirus, and influenza virus. The clinical manifestations of the viral myocarditis usually dominate over the clinical manifestations of the viral pericarditis. The typical signs and symptoms of acute viral pericarditis include a low-grade temperature, chest pain, and a frictional rub. The therapy for acute viral pericarditis is symptomatic. This includes bedrest, in particular patients who also have myocarditis. The prognosis of viral pericarditis is good and often self-limiting, with complete recovery in 3 to 4 weeks.

Similar to the adult pericarditis following a myocardial infarction, known as Dressler's syndrome, an episode of acute pericarditis in children following cardiac surgery which includes opening of the pericardium (post-pericardiotomy syndrome). The pathogenesis is unclear, however anti-myocardial antibodies and eosinophilia point toward an autoimmune etiology. Cardiac tamponade may occur, which may be treated with a pericardiocentesis, however in most cases of post-pericardiotomy syndrome, the disease is self-limiting in 2 to 3 weeks. The most important treatment is bedrest. Salicylates may be used to lower the temperatures and chest pain. In the severely ill child, a course of prednisolone may be effective.

Questions and Answers

1. What is the most common microorganism found in pediatric infective endocarditis?
    a. Staph aureus.
    b. Strep viridans
    c. E. coli
    d. Pneumococci
    e. Strep pyogenes

2. What is the preferred antibiotic treatment for the microorganism in question 1?
    a. Penicillin G x 2 weeks
    b. Penicillin G x 4 weeks
    c. Oxacillin x 6 weeks

3. Which microorganism(s) will most likely NOT manifest as an acute infective endocarditis in the pediatric setting?
   a. S. aureus
   b. Neisseria
   c. Strep. pyogenes
   d. HACEK (Haemophilus species (H. parainfluenzae, H. aphrophilus, and H. paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella species).

4. Does the pediatric case presented at the beginning of this chapter meet the Duke Criteria for Diagnosis of infective endocarditis?
   a. Yes.
   b. No.
   c. Need more information.

5. What type of prophylactic antibiotic against infective endocarditis would you prescribe to a nine-year old female, with a past medical history only remarkable for an allergic reaction to penicillin, scheduled for a tooth extraction the next day?
   a. Amoxicillin.
   b. Ampicillin.
   c. Clindamycin.
   d. Cefazolin.
   e. None.

6. What is the most common microorganism that causes pediatric infectious myocarditis in the United States?
   a. Strep viridans.
   b. Tuberculosis.
   c. Staph aureus.
   d. E. coli.
   e. Virus.

7. Which of the following answer is the most severe clinical manifestation commonly found in pediatric myocarditis?
   a. Myocardial infarction.
   b. Heart failure.
   c. Pericarditis.
   d. SLE.
   e. None of the above.

8. Which is the most helpful test to diagnose pericarditis?
   a. Cardiac enzymes.
   b. EKG.
   c. Echocardiogram.
   d. X-ray of the heart silhouette.
   e. Answers b and d.

9. Which of the following is/are treatments options for pediatric postpericardiotomy syndrome?
   a. Salicylates.
   b. Pericardiocentesis.
   c. Bed rest.
   d. Prednisolone.
   e. All of the above.

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Answers to questions

1. b.
2. b. Choice a is too short of a course and choice c is the preferred treatment for S. aureus infective endocarditis.
3. d.
4. a. The patient had positive blood cultures (1 major), and (3 minors) fever greater than 38 degrees C, a predisposing structural cardiovascular lesion (VSD), and evidence of an immunologic phenomenon (microscopic hematuria).
5. e. No antibiotics are needed, because this particular patient has no risk factors for infective endocarditis.
6. e.
7. b. Although c may be associated with viral myocarditis, viral pericarditis is most likely self-limiting.
8. c. Answers b and d may not show any abnormal findings.
9. e.

Chapter VII.6. Arrhythmias
Lance K. Shirai, MD

This is a 1 month old male who presents to the emergency room with a chief complaint of fever, lethargy, and poor feeding for the past 36 hours. He was well until he developed a tactile fever. His parents began noticing increasing lethargy and tiring with feeding and decreased oral intake for about 12 hours prior to presentation.

He is the product of a G2P1, full term, uncomplicated pregnancy. Delivery and stay in the nursery was uneventful.

Exam: VS T 38.0, HR 240, RR 72, BP 87/64, oxygen saturation 98% in room air. He is well developed, well nourished, but pale, lethargic and tachypneic, with mild subcostal retractions. HEENT exam is normal. Neck is supple without adenopathy. Lungs are clear to auscultation with good aeration. His heart is tachycardic with a regular rhythm. No murmur, rub, or valve clicks are heard. There is a soft S3 gallop that can be head from the lower left sternal border to the cardiac apex. His abdomen is soft, non-distended, non-tender, and without masses. His liver is 2 to 3 cm below right costal margin. His feet and hands are cool. His peripheral pulses are 1+ to 2+ (out of 4+) throughout. Capillary refill time is 3 to 4 seconds. He has no rashes or other significant lesions.

A chest x-ray shows mild cardiomegaly and mild pulmonary edema. A 12 lead electrocardiogram shows a narrow complex tachycardia (rate of 240 bpm) with no visible P-waves. Mild ST segment depression in the inferior-lateral leads is present.

The patient is felt to be in supraventricular tachycardia and mild congestive heart failure. A peripheral IV is started and he is given a rapid IV bolus dose of adenosine. The patient immediately becomes briefly bradycardic followed by resumption of a normal sinus rhythm at a rate of 140 beats per minute. He is admitted for overnight observation and initiation of an anti-arrhythmic medication. A 12 lead electrocardiogram following conversion shows no evidence of a delta-wave, so a loading dose of digoxin is administered.

An irregular heart rhythm is not an unusual finding in children with or without known cardiac disease. Some irregular rhythms are normal findings in healthy children. If the heart rate is not too slow or too fast, as to limit the cardiac output, then an arrhythmia may be well tolerated. Most children can be satisfactorily evaluated with a 12 lead electrocardiogram and rhythm strip, with possible supplementation by a chest x-ray, echocardiogram, Holter or event monitor, or an exercise study. There are several important determinants of arrhythmias, which should be considered. These include the arrhythmogenic substrate (e.g., accessory conduction pathway, automatic ectopic focus), modulating factors, and triggers of the arrhythmia.

Changes in sinus rhythm (P-wave preceding each QRS complex, with a normal P-wave axis) are most commonly seen with a sinus arrhythmia, sinus bradycardia, or sinus tachycardia. In pediatrics, a sinus arrhythmia is usually secondary to a variation in vagal tone during the normal respiratory cycle. This causes an increase in heart rate during inspiration and a decrease in heart rate during exhalation. It is most pronounced when the heart rate is slower and resolves with an increase in heart rate. Sinus bradycardia is a sinus rhythm with a rate below the lower normal limits for age and activity level. It is most often encountered in well conditioned athletes. Pathologic states in which sinus bradycardia may occur include increased intracranial, intrathoracic, or intraabdominal pressure, and systemic hypertension. Sinus tachycardia is a sinus rhythm with a rate greater than the higher limits for age and activity level. If the child is not active then the tachycardia usually has a secondary cause such as fever, heart failure, pain, anxiety, hypovolemia, anemia, myocarditis, or thyrotoxicosis.

Supraventricular tachycardia (SVT), also known as paroxysmal supraventricular tachycardia (PSVT) is a tachyarrhythmia manifesting with a narrow complex QRS duration (<0.08 sec). Many definitions of SVT exist, some of, which include all abnormal tachycardias originating in or around the atria (which would include PSVT, atrial fibrillation and atrial flutter). For the sake of this discussion, SVT will be defined as those narrow complex tachycardias involving the SA node and an accessory electrical pathway anywhere along the atrioventricular junction or very near the AV node itself (this definition excludes atrial fibrillation and atrial flutter). These are considered reciprocating tachycardias, as two discrete pathways are present, one with antegrade conduction and the other with retrograde conduction. One pathway is considered a "fast" pathway, with rapid conduction, and the other a "slow" pathway, with slower conduction. This creates the reentrant circuit. With orthodromic (conventional pathway) SVT, the antegrade conduction is down the "slow" pathway, usually the AV node, and the retrograde conduction is up the "fast" pathway, usually the accessory conduction tissue. Antidromic SVT is characterized by antegrade conduction down the "fast" pathway, and retrograde conduction up the "slow" pathway.

Supraventricular tachycardia is the most common abnormal tachycardia in the pediatric age group. The most common types of SVT in children include atrioventricular reentrant tachycardia (AVRT), which includes Wolff-Parkinson-White syndrome (WPW), and AV nodal reentrant tachycardia (AVNRT formerly called Lown-Ganong-Levine or LGL syndrome).

Supraventricular tachycardia usually has its onset at rest but may initiate during exercise. The precipitating factor(s) is often difficult to identify, but occasionally a febrile illness may precipitate an episode. The heart rate is usually in the 160 to 300 beat/min range. In general, the younger the patient the more rapid the SVT heart rate, but the longer the tachycardia is tolerated before symptoms (usually congestive heart failure) become obvious. As a rule, episodes of SVT onset and terminate abruptly, and may last anywhere from a few minutes to many hours, which is why it is called paroxysmal.

In infants, symptoms of SVT may not become apparent until the patient has been in SVT for 24 hours, or longer. They will often present with symptoms of congestive heart failure such as tachypnea, pallor, poor feeding, fussiness or lethargy.

In children and adolescents, symptoms may include palpitations, chest pain, shortness of breath, dizziness, syncope or near syncope, pallor, and diaphoresis. It is unusual for older patients to present in heart failure, as they will usually become symptomatic soon after the onset of SVT. They will often complain of intermittent episodes of palpitations, with mild associated symptoms.

Supraventricular tachycardia may present as syncope or near syncope. This may occur in patients with WPW who develop atrial fibrillation and rapid conduction down the accessory pathway to the ventricles. The onset of SVT can also cause a decrease in cardiac output with resultant hypotension, decreased cerebral perfusion pressure, and syncope. In the pediatric age group, the most common cause of syncope is neurocardiogenic syncope (also called a vasovagal faint). Syncopal episodes associated with palpitations should raise the suspicion of a possible tachyarrhythmia contributing to the patients symptoms. Nearly any type of cardiac arrhythmia can cause syncope if a sudden fall in cardiac output occurs. Cardiac dysrhythmias to consider should include SVT, ventricular tachycardia (in particular, long QT syndrome), advance degree AV block, sick sinus syndrome in patients with previous cardiac surgery, and pacemaker malfunction in those patients who are pacer dependent. Other cardiac related disease to consider in patients presenting with syncope include outflow tract obstruction (hypertrophic cardiomyopathy, aortic stenosis, pulmonic stenosis, pulmonary hypertension), coronary artery anomalies, cardiomyopathies, and mitral valve prolapse. The diagnosis can often be made with a thorough history and physical examination performed as close to the time of the syncopal episode as possible. Cases, which should arouse increased concern, include those not consistent with neurocardiogenic syncope, syncope with exercise, a family history of sudden death, and those patients with known

structural cardiac disease. All patients who present with syncope should, at the minimum, have an EKG performed. In most cases of neurocardiogenic syncope, symptoms will improve or resolve with increased fluid and salt intake. Treatment for other causes of syncope should address the underlying etiology.

The differential diagnosis of a pediatric patient who presents in a narrow complex tachycardia includes SVT, sinus tachycardia, atrial flutter, atrial fibrillation, junctional ectopic tachycardia, ectopic atrial tachycardia, and chaotic atrial rhythm. Some patients with SVT and a bundle branch block or antidromic WPW, may present with a wide complex tachycardia, which if often difficult to distinguish from ventricular tachycardia (VT).

Most of the narrow complex tachyarrhythmias may be distinguished from their electrocardiogram findings. Supraventricular tachycardia ranges in heart rate from 160 to 300 beats per minute. The diagnosis of AVRT or AVNRT requires the presence of 1:1 A-V conduction. The heart rate usually remains in a very narrow range regardless of the patient's physiologic state. P-waves, which are oftentimes retrograde, are visible only in 50% or less of cases. Upon conversion to a sinus rhythm, patients with WPW or Mahaim fibers (an accessory pathway able to conduct only antegrade, with slow conduction, connecting the atrium directly to a portion of the right bundle branch) will demonstrate the classical delta waves as evidenced by an upsloping or slurring of the initial portion of the QRS complex. Delta waves are secondary to rapid antegrade conduction from the atrium to the ventricles through the accessory pathway, thus causing ventricular pre-excitation. With WPW the PR interval is short, but with the presence of Mahaim fibers the PR interval is normal. Forms of SVT with concealed accessory pathways (i.e., those capable of only retrograde conduction), will not show evidence of a delta wave, and therefore most will have normal PR intervals. An exception is those patients with James fibers (a form of AVNRT), who have a short PR interval. Most patients with SVT have normal cardiac anatomy. Congenital heart defects in which SVT is most commonly encountered are Ebstein's anomaly and L-transposition of the great arteries.

Atrial flutter may present with a regular or regularly irregular tachycardia with an atrial rate in the range of 250 to 400 beats per minutes. The classic sawtooth flutter waves may be seen, or revealed following a dose of adenosine. The ventricular rate will depend on the degree of A-V conduction (e.g. 2:1, 3:1, etc.). Atrial flutter will most often be encountered in the setting of congenital heart disease, presence of significant mitral or tricuspid valve regurgitation with atrial dilatation, fetuses or newborns with normal hearts (i.e., it sometimes occurs in normal fetuses and newborns), or in patients with myocarditis.

Atrial fibrillation demonstrates a rapid atrial rate (300-500 beats per minute) with a very chaotic pattern, and an irregularly irregular ventricular rhythm. Atrial fibrillation is most often seen in older children following palliative surgery for congenital heart defects, especially those involving intra-atrial surgery (e.g., Fontan, Mustard, or Senning procedures), and those children with significant atrioventricular valve disease.

Ectopic atrial tachycardia and chaotic atrial rhythm are rare tachyarrhythmias in the pediatric age group. On EKG, ectopic atrial tachycardia will show the presence of a variable atrial rate with an abnormal P-wave axis indicating a single atrial focus. Chaotic atrial rhythm, also referred to as multifocal atrial tachycardia, typically demonstrates at least 3 non-sinus P-wave morphologies, an irregular ventricular response, and variable PR, PP, and RR intervals. Both types of dysrhythmias occur most often in patients with structurally normal hearts, at times with concomitant myocarditis.

Junctional ectopic tachycardia is most commonly encountered in children less than 2 years of age, in the immediate post-operative period following corrective surgery for a congenital heart defect involving the region around the AV node (e.g., a VSD or tetralogy of Fallot repair). This is one of the most common post-operative arrhythmias encountered. The EKG typically demonstrates a narrow complex tachycardia with a regular atrial and ventricular rhythm, and a ventricular rate, which is more rapid than the atrial rate. This dysrhythmia originates from a focus of enhanced automaticity in the peri-AV nodal region. The heart rate typically rises and decreases gradually (warms up and cools down). This feature helps differentiate it from a reentrant type of tachyarrhythmia.

Significant ventricular arrhythmias, such at ventricular tachycardia (VT) and ventricular fibrillation (VF), are rarely encountered in the pediatric age group. Benign premature ventricular contractions (PVC) are not uncommon in infants, older children, and adolescents. Patients with ventricular arrhythmias may be asymptomatic or they may present with symptoms of palpitations, chest pain, dizziness, and/or syncope. Ventricular tachycardia is defined at 3 or more consecutive abnormal QRS complexes at a rate greater than 120 beats per minute. As mentioned previously, SVT may occasionally present as a wide complex tachycardia, which may be difficult to distinguish from ventricular tachycardia. In these cases, the definitive diagnosis may not be known until the patient is converted to a sinus rhythm. In these situations the patient should be presumptively treated as having ventricular tachycardia (VT) until proven otherwise. It should be remembered that VT does not always present as a wide QRS complex tachycardia, especially in infants. Ventricular fibrillation displays unidentifiable QRS complexes due to an uncoordinated state of ventricular depolarization, resulting in a state of poor cardiac output. Significant ventricular dysrhythmias in the pediatric age range are most commonly encountered in the setting of congenital heart disease, myocarditis, cardiomyopathies, myocardial trauma, hypoxia, acidosis, and electrolyte abnormalities (most notably hypokalemia and hyperkalemia).

The prolonged QT syndrome causes a distinct type of VT called Torsades de Pointes characterized by a polymorphic VT, which oftentimes causes syncope or sudden death. Recent genetic linkage analyses have isolated a number of genetic foci associated with defects in cardiac ion channels (namely sodium and potassium channels). Prior to the advent of genetic analysis, patients with long QT syndrome were classified into two groups: Jervell-Lange-Nielsen (autosomal recessive, associated with congenital deafness) and Romano-Ward (autosomal dominant, without deafness). Prolongation of the QT interval may also develop secondary to drugs (anti-arrhythmic agents, antihistamines, antidepressants, antipsychotics, some antibiotics), CNS trauma, cardiomegaly, hypokalemia, and hypocalcemia.

Various forms of heart block are usually encountered in children with congenital heart defects, heart failure, or with congenitally acquired heart block. Congenital complete heart block is most commonly seen in the setting of a maternal collagen vascular disorder, namely systemic lupus erythematosus or Sjogren's syndrome. In nearly all cases, maternal SS-A/Ro and SS-B/La autoantibodies can be isolated. Conversely, not all fetuses whose mother is positive for these antibodies will develop heart block. The most common congenital heart defect associated with complete heart block is L-transposition of the great arteries. If the ventricular rate is too slow to maintain adequate cardiac output, heart failure may develop in utero or postnatally. Treatment involves permanent pacing. The decision to treat depends on the baseline ventricular rate and the likelihood of sudden death.

The management approach for SVT depends upon the age and condition of the patient on presentation. If the patient is clinically stable, vagal maneuvers may be initially attempted to convert the tachycardia. Such vagal maneuvers may include bearing down (as though having a bowel movement, i.e., Valsalva maneuver), or inducing the diving reflex using an ice bag to the face or submerging the patient's face into a container of ice water. Other vagal maneuvers such as eyeball pressure and unilateral carotid massage are less effective and may be harmful.

If the patient appears clinically unstable, then an intravenous line should be immediately started in a centrally located peripheral vein (antecubital preferred over a hand vein) through which an IV bolus of adenosine may be given. It must be remembered that this medication has a very short half life of approximately 10 seconds, therefore it should be administered via bolus injection followed by an immediate bolus of saline utilizing either a 3 way stopcock or simultaneous needles within the same IV hub (the IV push and immediate flush technique). A 12 lead electrocardiogram should be obtained before and after conversion, if possible, and a rhythm strip should be continuously run during attempted conversion. External pacing equipment should be available since some patients go into sinus arrest following administration of adenosine. Adenosine causes a transient AV block and sinus bradycardia thus interrupting the reentrant circuit involving the AV node and accessory pathway. Potential side effects with adenosine include hypotension, bronchospasm, and flushing.

In rare cases, a patient will present in very unstable condition. Immediate electrical cardioversion may be required in such cases, especially if an IV cannot be started in an expedient manner or the patient fails to convert with IV adenosine.

Other modes of acute treatment include use of digoxin, verapamil, propranolol, transesophageal or transvenous pacing. Conversion to a sinus rhythm with these medications will usually be slower, therefore most are utilized for chronic control once the SVT has been converted by other means. If adenosine fails to convert the SVT, but the patient is hemodynamically stable, they may be started on one, or more, of these medications (with the exception of verapamil which should be avoided in infants) and monitored for conversion. It is important to remember not to use digoxin on patients with ventricular pre-excitation (e.g., WPW), as it may increase antegrade conduction down the accessory pathway. Patients with WPW are more prone to develop atrial flutter or fibrillation, and are therefore at risk for 1:1 conduction to the ventricles while on digoxin, potentially sending the patient into ventricular tachycardia or fibrillation.

Long term management of SVT depends on the severity and frequency of episodes. In those patients with no ventricular pre-excitation and infrequent, mild episodes that can be converted with vagal maneuvers, no treatment is required. Patients with frequent episodes, or severe symptoms, and those with ventricular pre-excitation, medical management should be started with a beta-blocker, digoxin, or calcium channel blocker. Patients diagnosed in infancy often will not require continued treatment beyond 1 year of age, but may have recurrent episodes later in life. With the presence of severe symptoms, syncope, difficult to control SVT, or other situations, e.g., patient preference, an electrophysiology study and radiofrequency ablation can be performed with a high success rate for cure.

The majority of fetuses and infants who present in SVT will have no recurrences off medication after 6 to 12 months of age. Patients who present in later childhood or during adolescence will likely have recurrent episodes of SVT throughout their lifetime. Many of these patients will require medical treatment and will eventually seek curative treatment with radiofrequency ablation. Radiofrequency ablation involves mapping out accessory conduction pathways in the heart with the use of electrodes placed in the atria, coronary sinus, and ventricles through central venous access. Upon localization of the pathway a specialized ablation catheter (tip is heated using radiofrequency energy) is used to burn and cause irreversible tissue injury to the accessory conduction tissue.

With the recent advancements in pediatric electrophysiology, the prognosis for patients with SVT is very good. The success rate with radiofrequency ablation continues to improve, especially when performed at centers with experienced specialists. Death or significant morbidity is rare with the present state of medical management. Most patients can be expected to live a normal life expectancy with little or no lifestyle alteration due to this condition.

Questions

1. What are the two most common forms of SVT in the pediatric population?
2. What are the two most common types of congenital heart defects associated with SVT?
3. Name two instances in which SVT may present as a wide complex QRS tachycardia.
4. In a hemodynamically stable patient who presents with SVT, what are the two most commonly used methods for attempted conversion to a sinus rhythm?
5. True/False: Supraventricular tachycardia is the most common cause of syncope in the pediatric age group.

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Answers to questions

1. Atrioventricular reentrant tachycardia (AVRT) and AV nodal reentrant tachycardia (AVNRT).
2. Ebstein anomaly and L-transposition of the great vessels.
3. With the presence of a bundle branch block or with antidromic conduction.
4. Vagal maneuvers and intravenous adenosine.
5. False.

Chapter VII.7. Vascular Rings and Slings
Cheryl M. Takao, MD

This is a 6 week old male with a previous diagnosis of laryngomalacia who presents with increasing stridor, respiratory distress and wheezing. There has been no associated apnea or cyanosis. He had been feeding well with no vomiting or choking. He has had no fever. Initial CXR revealed no acute infiltrates. He received albuterol but had a minimal response.

He was born at term via NSVD with 8 and 9 Apgars. No intubation required. Mild respiratory distress was noted on his first day of life. A CXR revealed fluid within fissures. O2 sat on RA was 98%, so transient tachypnea of the newborn was initially suspected. On the second day of life, he was noted to have stridor. He was evaluated by ENT surgeon with a flexible bronchoscopy which revealed mild laryngomalacia. His condition improved and he was discharged home in stable condition.

Family history: Father, 12 y.o. brother, 7 y.o. and 18 month old sister with asthma.

Exam: VS T 37.1, HR 160, RR 52, BP 109/56, oxygen saturation in RA 98%. Wt. 5.3kg (75%), ht 52.5cm (10%), HC 39.5cm (90%). He is lying in mother's arms, visibly tachypneic, with audible congestion. HEENT and neck exams are normal. Heart RRR, with gr II/VI systolic ejection murmur at the left sternal border. Lung exam shows inspiratory and expiratory stridor, coarse BS, diffuse wheezes, subcostal retractions. Abdomen is benign without organomegaly. Femoral pulses are 2+ bilaterally. No skin rashes are noted. His color is pink and his perfusion is good. No neurologic abnormalities are noted.

A CXR is obtained which shows clear lung fields. Close examination of the trachea on the lateral view shows that the trachea is narrowed and it appears to be bowed anteriorly. Coupled with the clinical findings (airway symptoms since birth, current presentation with stridor), these findings raise the suspicion of tracheal compression, such as with a vascular ring. He is treated with bronchodilators, racemic epinephrine and suctioning for his acute symptoms. A CT of the chest reveals findings suspicious for a double aortic arch and an esophagram reveals a posterior indentation on the esophagus. MRI and MRA studies confirm the diagnosis of a double aortic arch (the aorta ascends and splits such that one arch travels anterior to the trachea and over the left mainstem bronchus, while the other arch travels over the right mainstem bronchus and posterior to the esophagus and trachea, at which point, both branches join together to form the descending aorta). Echocardiography also suggests a double aortic arch. He undergoes a surgical correction and postoperatively he improves, but he continues to have mild stridor. Bronchoscopy reveals mild tracheal stenosis.

Vascular rings and pulmonary slings are congenital anomalies of the aortic arch and pulmonary artery. They are very important but rare causes for common respiratory symptoms. They arise from abnormal embryonic development of the aortic arches. When the abnormal blood vessels encircle the trachea and esophagus, it is termed a vascular ring. These rings may be complete or incomplete. The severity of symptoms depend on the degree of compression on the trachea and esophagus.

Multiple paired branchial arches and paired dorsal aorta sequentially fuse and resorb in embryonic development. This results in a left aortic arch (i.e., the aortic arch travels over the left mainstem bronchus) and left descending aorta. Failure of regression or persistence of normally regressed portions will result in one of many vascular rings or a pulmonary artery sling.

Paired right and left dorsal aorta are present in an embryo at approximately 21 days. They come together at the aortic sac. Six branchial arches form along with its own aortic arches that communicate with the aortic sac. The appearance and regression of the aortic arches follow the number they are assigned. The 1st aortic arch is the 1st to appear and the 1st to regress. The 1st and 2nd aortic arch form the maxillary and hyoid/stapedial arteries respectively. The 3rd arch becomes the common carotid arteries. The 4th arch forms the proximal portion of the subclavian on the right and the aortic arch segment on the left. The 5th arch has no known derivatives. The 6th arch develops into the pulmonary arteries.

Edwards was the first to describe embryonic pathophysiologic mechanisms in 1948. Vascular rings will result from disruption at 4 points in the normal development. The 1st point is at the right dorsal aorta. This normally will regress but if it persists, a double aortic arch will develop. The 2nd point is at the right 4th aortic arch. This normally will persist and develop into the proximal portion of the subclavian artery on the right. Failure of this to develop will result in the right subclavian artery to arise from the left aortic arch. The 3rd point is at the left dorsal aorta. This normally persists to form the left descending aorta. If this regresses, a right aortic arch will persist. The 4th point is at the left 4th arch. This normally persists and develops into a portion of the left aortic arch. If this regresses, a right aortic arch will persist and the left subclavian will arise from the right arch.

Vascular rings encompass only 1% of all congenital heart disease. Some vascular rings are associated with other congenital heart lesions while others are isolated defects. Tracheobronchial anomalies are seen with vascular rings but are more highly associated with pulmonary artery slings.

The most common symptomatic vascular ring is the double aortic arch. This results from persistence of the right dorsal aorta. The right and left aortic arches encircle the trachea and esophagus. 70-90% have a dominant right aortic arch with the left arch hypoplastic or atretic. The aorta ascends from the heart and splits such that one arch travels anterior to the trachea and over the left mainstem bronchus, while the other arch travels over the right mainstem bronchus and posterior to the esophagus and trachea, at which point, both branches join together to form the descending aorta. The double aortic arch forms a ring around the trachea and esophagus (hence the term vascular ring) compressing both the trachea and esophagus. Tracheoesophageal compression will result in early symptoms. This type of vascular ring is rarely associated with intracardiac defects.

The second most common vascular ring is the right aortic arch, aberrant left subclavian with a left ligamentum arteriosum. In this malformation, the aorta ascends from the heart anterior to the tracheal bifurcation, to arch over the right mainstem bronchus. It then descends posterior to the esophagus and trachea. The left subclavian comes off the descending aorta. The ligamentum arteriosum (remnant of the ductus arteriosus) connects the left subclavian or descending aorta (depending on its origin) to the left pulmonary artery. The trachea and esophagus are encircled by the ascending aorta anteriorly, the aortic arch on the right, the descending aorta posteriorly, and the ligamentum arteriosum and the left pulmonary artery on the left. This results from persistence of the right dorsal aorta, regression of the left dorsal aorta and regression at the left 4th aortic arch. Due to the regression of the 4th arch, the left subclavian develops from the right descending aorta. 10% of this type of ring will have associated intracardiac defects.

A third type of vascular ring is the right aortic arch with mirror branching vessels. It results from persistence of the right dorsal aorta and regression of the left dorsal aorta. A complete ring is completed only if the ductus arises from the upper descending aorta. If the ductus arises from the left subclavian, an incomplete ring is formed. This type of vascular ring has greater than 90% association with intracardiac defects. This can be explained by the hemodynamics in developing hearts. Normally, formation of a vessel occurs as a result of blood flow through it. In a normally structured heart, blood is ejected to the left side stimulating the formation of the left arch. If there

is abnormal blood flow due to internal structure such that blood is ejected to the right, persistence of the right arch will develop. Approximately 25% will have tetralogy of Fallot, 20% will have double outlet right ventricle and 25% will have truncus arteriosus.

A fourth type of vascular ring is the left aortic arch and aberrant right subclavian artery. This results from the regression of the right 4th arch which normally develops into the proximal portion of the right subclavian. The right subclavian now arises as the last branch on the left aortic arch. The aberrant right subclavian travels posterior to the esophagus to the right side. This type of vascular ring is incomplete and symptoms are minimal. It is occasionally associated with dysphagia occurring in adolescents or adulthood. This has a higher association with coarctation of the aorta.

A pulmonary sling is the left pulmonary artery arising from the right pulmonary artery. This is also known as anomalous pulmonary artery. This results from regression/failure of development of the left pulmonary artery. As the lung buds on each side develop, the right pulmonary artery is stimulated to form collaterals to the left lung. The collaterals eventually enlarge to provide blood flow to the developing left lung, acting as the left pulmonary artery. The pulmonary artery travels between the trachea and esophagus as it arrives on the left side. Most of these patients are symptomatic by 1 month of age. Respiratory symptoms predominate as the compression is most severe on the trachea. 50% of these patients also have severe tracheobronchial anomalies such as tracheomalacia, stenosis, webs, complete tracheal cartilage rings called "O" rings (as opposed to the normal "C" cartilage rings) or long segmental stenosis. This anomaly also is associated with intracardiac defects present in 10-20%.

Respiratory symptoms predominate in initial presentation. These symptoms occur from tracheobronchial compression from the vascular ring or pulmonary sling. The severity of compression determines the severity of symptoms. 70-97% of patients will have respiratory symptoms. Stridor is present in 97% of cases. 65% will present on the first day of life. Stridor may be more pronounced during feeding or activity. Wheezing, air trapping and hyperinflation are also common. Many infants may have recurrent pneumonias. Diagnosis is difficult due to the rarity of these anomalies and the common symptoms these infants exhibit. Many of the patients will have a delay in diagnosis due to attribution of symptoms to other more common etiologies and the difficulty of establishing this diagnosis without an advanced imaging study such as CT, MRI, echocardiography, or esophagram. Most infants are diagnosed by age 12 months. The most common cause of stridor is laryngomalacia. This also is seen at birth and can easily mask symptoms from a vascular ring.

Symptoms of dysphagia are less common. This occurs from compression of the esophagus posteriorly from the vascular ring. 5-15 % of patients will have dysphagia alone. Symptoms include slow breast or bottle feeding, fatigue with feeding, frequent regurgitation and aspiration pneumonias. Many times the diagnosis is made when solid foods are introduced and dysphagia symptoms are more pronounced.

Again, the more severe the compression, the more severe the symptoms and the earlier age of presentation. Double aortic arch, right aortic arch with left ligamentum arteriosum and anomalous pulmonary artery present early in infancy. Aberrant left subclavian artery may be clinically silent or present in adolescence/adulthood with dysphagia.

Evaluation of suspected vascular rings should include a chest x-ray, esophagram, echocardiogram and a CT or MRI. There is much debate on the radiographic evaluation for vascular rings due to the advancement in radiographic studies. While CXRs are frequently done, the signs of a vascular ring are usually too subtle to be routinely diagnostic. A positive esophagram may provide supporting evidence of a vascular ring, but the other imaging modalities are superior.

There are subtle characteristics of CXR findings for each type of vascular ring. An anterior indentation of the trachea at or above the carina on a lateral film suggests a complete ring or anomalous innominate artery (not discussed in this chapter). A right sided aortic arch may suggest a vascular ring and this can occasionally be suspected if the distal trachea is slightly deviated to the left (due to the aorta arching over the right mainstem bronchus). Hyperinflation of the left lung with the left hilum lower than the right suggests a pulmonary sling.

Echocardiography is useful in evaluating for associated intracardiac defects. It is possible but difficult to completely delineate the anatomy of the vascular ring on the echocardiogram alone.

Bronchoscopy is useful when there is suspicion of tracheobronchial anomalies. Identification of these associated anomalies may assist the surgeon if correction of tracheal anomalies will be performed at the same time. If bronchoscopy is done prior to diagnosis, there are some characteristics of vascular rings. A pulsatile indentation may be seen on the anterior wall of the trachea. In a pulmonary sling, the pulsatile indentation may be on the right side or posterior.

CT scan can be used to identify structures in the thoracic cavity. It is fast and no sedation is usually required. It is however difficult to identify the ligamentum or an atretic branch of the aortic arch. MRI can more definitively identify the vascular ring as well as the tracheoesophageal anatomy. This however requires sedation and more time.

Angiography was used prior to the advancement in CT and MRI. It provides anatomy of the abnormal vessels and also identifies associated congenital heart defects. It fails to show atretic portions of vessels and is unable to identify nonvascular anomalies.

Vascular rings are surgically corrected if the patient is symptomatic. If the patient is asymptomatic or has mild symptoms, he/she can be monitored and treated conservatively. Many mild symptoms will resolve with growth. It is however necessary to surgically correct patients with pulmonary slings, double aortic arch and right arch with a left ligamentum arteriosum. These patients will progressively become more symptomatic over time.

Postoperatively, many patients will have respiratory symptoms related to tracheomalacia and airway obstruction. 10% of patients have symptoms that persist for months. This is expected to resolve with growth. In 95% of patients, surgical correction of the vascular ring is curative. Patients with pulmonary slings have a much higher percentage of tracheobronchial anomalies. Some of these patients will need further surgery to correct their tracheal anomalies.

In summary, the diagnosis of a vascular ring or pulmonary sling requires a high index of suspicion. CXR and esophagram may be used for the initial work up, but further anatomic details are obtained by echocardiography, CT/MRI or bronchoscopy for tracheal anomalies. Early surgical correction is safe and effective. Mild respiratory symptoms persist postoperatively but are expected to resolve.

Questions

1. Which vascular anomaly will exhibit a complete vascular ring?
    a. right aortic arch, mirror branching, left ligamentum from left subclavian
    b. right aortic arch, aberrant left subclavian
    c. left aortic arch, aberrant right subclavian
    d. pulmonary sling

2. Which vascular anomaly may present in adolescence or adulthood with dysphagia?
    a. double aortic arch
    b. right aortic arch, aberrant left subclavian
    c. left aortic arch, aberrant right subclavian
    d. pulmonary sling

3. What vascular anomaly is most associated with severe tracheobronchial anomalies?
    a. Right aortic arch, left subclavian
    b. Double aortic arch
    c. Pulmonary artery sling
    d. All of the above

4. All of the following are common symptoms of vascular rings except:
    a. wheezing
    b. hoarse cry
    c. stridor
    d. dysphagia

5. All of the following studies could find evidence to support the diagnosis of a suspected vascular ring except:
    a. Esophagram
    b. Pulmonary function tests
    c. CXR
    d. Echocardiogram

6. Describe the structures which form the vascular ring in a double aortic arch.

7. Describe the differences between a vascular ring and a vascular sling.

Related x-rays

X-rays and diagrams of vascular ring case: Yamamoto LG. Difficulty Breathing Throughout Infancy. In: Yamamoto LG, Inaba AS, DiMauro R. Radiology Cases In Pediatric Emergency Medicine, 1999, volume 6, case19. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v6c19.html

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Answers to questions

1.b, 2.c, 3.c, 4.b, 5.b

6. right aortic arch, left aortic arch, connecting to the descending aorta.

7. A vascular ring involves the aorta and its branches. A vascular sling involves the pulmonary artery. In the vascular sling, the left pulmonary artery arises from the right pulmonary artery and compresses the trachea posteriorly.

Chapter VIII.1. Interpretation of Blood Gases and Pulse Oximetry

Loren G. Yamamoto, MD, MPH, MBA

This is a 5 year old male with a history of fever and coughing. His temperature has been up to 40 degrees C (104 degrees F). He has been ill for three days. He has vomited 8 times today and 4 times yesterday. He is also weak and oral intake has been poor. His past medical history and family history are unremarkable.

Exam: VS T39.0, P140, R50, BP 100/70, oxygen saturation 93% in room air, height and weight 50th percentile. He is drowsy, in moderately severe respiratory distress, and mildly toxic in appearance. His eyes are clear but sunken. His TMs are normal. His oral mucosa is sticky. His neck is supple without adenopathy. Cardiac exam demonstrates tachycardia without murmurs. Lungs reveal coarse breath sounds without wheezing. Moderate retractions are present with obvious tachypnea. Abdomen is soft and non-tender. His color and perfusion are good. His neurologic exam is intact except for the fact that he is slightly weak.

A chest radiograph shows a right middle lobe infiltrate. A CBC is remarkable for a WBC of 28.5 with 15% bands, 65% segs, 15% lymphs, 5% monos. A chemistry panel shows Na 136, K3.6, Cl 100, bicarb 17, glucose 100. A blood culture is also drawn. An arterial blood gas obtained with the patient breathing room air shows pH 7.35, pCO2 33, pO2 80, BE -7, HCO3 16, O2sat 93%. He is placed on 6 L oxygen by mask, an IV fluid infusion is begun, and antibiotics are administered. His oxygen saturation increases to 100% while breathing supplemental oxygen.

A normal blood gas should be memorized using single values rather than a range: pH 7.40, pCO2 40, pO2 100, BE 0, HCO3 24. Our patient's arterial blood gas (ABG) shows that the partial pressure of oxygen (pO2) is slightly low, but satisfactory. Once supplementary oxygen is administered, his oxygenation improves as demonstrated by a rise in oxygen saturation. His ABG also shows that he has a metabolic acidosis (high negative base excess-BE and low bicarbonate). He has partial respiratory compensation since his low pCO2 partially offsets the metabolic acidosis.

An arterial blood gas (ABG) measures three components: pH, pCO2, pO2. All the other numbers on a blood gas are calculated. The bicarbonate (HCO3) value is calculated based on the measured pH and the measured pCO2, using the Henderson-Hasselbalch equation. The base excess (BE) is calculated using a similar equation. The oxygen saturation is calculated based on the assumption that normal adult hemoglobin (HgbA) is the dominant hemoglobin in the sample (using the oxygen hemoglobin dissociation curve).

The pH measures the net circulating acid/base level. The pH can be affected by ventilation and by metabolic factors. Although the Henderson-Hasselbalch equation relates the pH, pCO2 and the HCO3 (bicarbonate, bicarb for short) values, suggesting that the three are in a dynamic equilibrium, it is easiest to interpret a blood gas based on the assumption that pCO2 and HCO3 are independent contributors to the pH. As the bicarb goes up, the pH goes up (less acidic, more alkaline). As the pCO2 goes up, the pH goes down (more acidic). The pCO2 determines the respiratory component of the pH, while the bicarb determines the metabolic component of the pH. The pCO2 and the bicarb contribute to the acidosis in opposite directions.

Even though we learned in chemistry that a pH of 7.0 is neutral, this is not the same for biological systems. The human body functions best at a pH of 7.40. Human proteins, hence cellular function, have reduced bioactivity at a pH outside of this value. Anything less than 7.40 is an acidosis. Anything above 7.40 is an alkalosis.

Table 1 below lists several ABG examples to help us. The interpretation of blood gases should be done in conjunction with the patient's clinical status.

	pH	pCO2	pO2	Bicarb	BE
A	7.40	40	100	24	0
B	7.22	60	70	24	-3
C	7.04	60	70	16	-13
D	7.31	60	80	30	+4
E	7.26	34	100	15	-11

ABG-A is a normal blood gas in room air. ABG-B (pH 7.20, pCO2 60, pO2 70, bicarb 24, BE -3) shows a patient with acute respiratory failure. The pH is less than 7.40 which means that the patient has an acidosis. The pCO2 is very high so this is the respiratory component which contributes to the acidosis. The bicarb is normal (equivalent to saying that the base excess is 0). This is called a respiratory acidosis. The pCO2 is indicative of the minute ventilation, in other words, the amount of total air that is moved in and out of the lungs per unit time. The minute ventilation can be increased by increasing the respiratory rate or increasing the tidal volume or both. As the minute ventilation increases, the pCO2 will decrease. A high pCO2 signifies a decreased minute ventilation. Thus, in general, pCO2 = ventilation. A very high pCO2 in conjunction with a low pO2 (hypoxia) suggests acute respiratory failure. This patient is likely to be lethargic, with a poor respiratory effort. This patient requires prompt positive pressure ventilation by bag-mask ventilation and eventual tracheal intubation and mechanical ventilation.

If this patient is allowed to remain hypoxemic without any intervention, ABG-C (pH 7.04, pCO2 60, pO2 70, bicarb 16, BE -13) will result. Because the tissues are hypoxic for a prolonged period, they shift to anaerobic metabolism and generate lactic acid. Since bicarb is the dominant cellular and extracellular buffer, the bicarb will decline as metabolic acid levels increase. This ABG shows a worsening of the acidosis since both the respiratory and metabolic components are contributing to the acidosis.

ABG-D (pH 7.31, pCO2 60, pO2 80, bicarb 30, BE +4) shows a low pH, hence an acidosis. The pCO2 is high which causes an acidosis, so this is a respiratory acidosis. In chronic lung disease, such as in infants with bronchopulmonary dysplasia or adults with chronic emphysema, air exchange is chronically poor, thus pCO2 is chronically high. The kidneys sense the acidosis, and compensate by retaining bicarbonate to partially raise the pH. This is called metabolic (as opposed to respiratory) compensation. This does not occur acutely which is why ABG-B (acute respiratory failure) shows no metabolic compensation. Note that with the pCO2 of 60, and a normal bicarb (24), the pH is 7.22, but with the same pCO2 and a higher bicarb (30), the pH is closer to 7.40. ABG-D can be described as a respiratory acidosis with metabolic compensation.

Look at ABG-D again: pH 7.31, pCO2 60, pO2 80, bicarb 30, BE +4. Why couldn't we call this a metabolic alkalosis with secondary respiratory compensation? Because the pH is less than 7.40, this is an acidosis, not an alkalosis. Thus, since the metabolic factor should cause an alkalosis, but the pH shows an acidosis, this must be a respiratory acidosis, with secondary metabolic compensation.

ABG-E (pH 7.26, pCO2 34, pO2 100, bicarb 15, BE -11) is a patient with renal failure who requires hemodialysis every other day. Because his kidneys cannot excrete acid, he has a chronic metabolic acidosis (bicarb 15, BE -11). To compensate for this, the brain senses the acidosis and the brain's respiratory center stimulates the respiratory rate to cause a tachypnea, which increases the minute ventilation to increase the pH. ABG-E can be described as a metabolic acidosis with partial respiratory compensation. Why can't we call this a respiratory alkalosis with secondary metabolic compensation? Because the pH is less than 7.40, this is an acidosis, not an alkalosis. Thus, since the respiratory factor should cause an alkalosis, but the pH shows an acidosis, this must be a metabolic acidosis, with secondary respiratory compensation.

ABG-E, could also be seen in a dehydrated patient. The dehydration causes a metabolic acidosis, which causes some secondary tachypnea (respiratory compensation). The same thing occurs in diabetic ketoacidosis. But since the degree of acidosis is generally more severe, the degree of tachypnea is generally more exaggerated (Kussmaul respirations).

So far we have seen an example of: 1) a respiratory acidosis with metabolic compensation, and 2) a metabolic acidosis with respiratory compensation. Is it clinically possible to see other combinations? Specifically, could the following scenarios be possible: 3) a respiratory alkalosis with metabolic compensation and 4) a metabolic alkalosis with respiratory compensation.

A respiratory alkalosis could only be caused by increasing the minute ventilation. Clinically, this would have to be done by hyperventilating. Since metabolic compensation does not occur acutely, one would have to hyperventilate for a long time for metabolic compensation to occur. This would not be a realistic clinical condition. However, in a patient on a mechanical ventilator set such that the patient is deliberately hyperventilated for a prolonged period, the kidneys may sense the alkalosis and thus, excrete bicarb to partially compensate for this. An ABG example of this would be pH 7.41, pCO2 35, pO2 100, bicarb 22, BE -2. This would be an unusual case of a respiratory alkalosis with metabolic compensation.

The last possibility is a metabolic alkalosis with respiratory compensation. This is even less likely clinically. How can a patient develop a metabolic alkalosis? There are only a few possibilities: 1) The patient would have to take a drug which excretes chloride or retains bicarbonate. 2) The patient would have to consume excess amount of alkaline substances, such chronic antacid use. 3) The patient would have to be a chronic vomiter (e.g., bulimia nervosa) since chronic vomiting results in excessive hydrochloric acid loss. Do such patients develop respiratory compensation? To do this, they must hypoventilate!! This is possible, but not likely. This clinical situation is unlikely.

How do venous and capillary blood gasses differ from an arterial blood gas? Looking at the three blood gas measurements: 1) The venous bicarb and the arterial bicarb are roughly the same. 2) The venous pCO2 is slightly higher than the arterial pCO2 because additional CO2 is picked up from the tissues, but the difference between the two is rather small. 3) The venous pO2 is substantially lower than the arterial pO2.

Since only the pCO2 and the bicarb contribute to the pH, the venous pH and the arterial pH are roughly the same. A venous or a capillary blood gas very closely approximates the arterial pH, pCO2 and bicarb (or BE), under ideal conditions with well perfused tissues, but they do not approximate the arterial pO2. All that can be said about a venous pO2 is that it is lower than the arterial pO2. All that can be said about a capillary pO2 is that it lies somewhere between the venous pO2 and the arterial pO2. Fortunately, pulse oximetry accurately reflects the arterial pO2. Therefore, a venous blood gas or capillary blood gas done in conjunction with a pulse oximeter measurement, should accurately reflect the arterial blood gas as long as the capillary source is well perfused. Often, no blood gas is needed at all. The bicarb value can be obtained by ordering a standard set of electrolytes, the pO2 can be accurately estimated using a pulse oximeter, and the pCO2 can be clinically estimated using auscultation by listening for the degree of air exchange.

The arterial pO2 is frequently described as the paO2 to denote that this is an arterial sample, as opposed to a venous or capillary pO2. Blood gases and pulse oximeters can be occasionally fooled so it is important to know when these tests provide us with misleading information. It is important to understand the difference between the pO2, the oxygen saturation (often called SO2 or SaO2), the oxygen content and the oxygen delivery rate.

The pO2 represents the partial pressure of oxygen or the gas tension. This concept is difficult to visualize, but it can best be thought of as the force that the oxygen particles exert on the side of an enclosed container. Gases travel rapidly, so that the partial pressures of gases tend to be identical in samples that are next to each other for at least 5 seconds. Gas pressure or gas tension is measured in mmHg or Torr, which are exactly the same thing. The atmospheric pressure at sea level is 760 mmHg (or Torr) and the atmosphere contains 21% oxygen. Thus the pO2 that we breathe in is 160.

What is the pO2 in a cup of coffee? As the coffee sits on the table, its gas content rapidly equilibrates with the environment so the pO2 in the liquid coffee is 160 mmHg. If one sends a sample of coffee to the blood gas lab, the blood gas machine should measure a pO2 of 160. Normal pO2 in arterial blood is only 100 mmHg. If I replaced my blood with coffee, my brain and other tissues would not be happy since although the pO2 of the coffee may be 160, it does not contain much oxygen. Blood holds a lot of oxygen which is why we need blood. One ml of coffee contains only a few oxygen molecules, while one ml of blood contains many, many more oxygen molecules. Each hemoglobin molecule has four oxygen binding sites. Blood contains red blood cells and plasma. RBCs hold a lot of oxygen while the plasma contains only minute amounts of oxygen. The pO2 of RBCs is the same as the pO2 of the plasma, yet the oxygen content of the plasma is minute, compared to the oxygen content of RBCs. Substituting coffee for blood, is like removing all the RBCs and letting plasma alone flow though the body. This is the difference between pO2 and oxygen content. While many fluids may have reasonably good pO2s, only blood has a satisfactory oxygen content. The pO2 of a fluid sample is a measurement of its oxygen gas tension (or pressure), but it is not a measurement of oxygen content.

An oxygen saturation measurement can only be done on blood, as opposed to a pO2 which can be done on coffee or any fluid. The pO2 and the SaO2 are related to each other by the oxygen hemoglobin dissociation curve, which students learn in physiology. This curve plots the oxygen saturation (in %) on the vertical axis and pO2 on the horizontal axis. The oxygen saturation % steadily increases as the pO2 increases up to about a pO2 of 100 mmHg at which point the oxygen saturation is 99% to 100% (i.e., all the hemoglobin oxygen binding sites contain oxygen). If the patient breathes supplemental oxygen, the inspired pO2 increases to 200 mmHg, 400 mmHg or higher depending on how much oxygen is inhaled. Thus, a patient breathing supplemental oxygen may have a pO2 as high as 400 mmHg, but his oxygen saturation is still 100%, since it can't get any higher than this. So the typical appearance of an oxygen hemoglobin dissociation curve, has a steep rise at pO2s below 100 mmHg, at which point it becomes a plateau since the oxygen saturation cannot increase above 100%.

Oxygen saturation (SaO2) is a measurement of the percentage of oxygen binding sites that contain oxygen. If all the oxygen binding sites contain oxygen, then the oxygen saturation is 100%. An oxygen saturation measurement can only be done on blood, as opposed to a pO2 which can be done on coffee or any fluid. The pO2 and the SaO2 are related to each other by the oxygen hemoglobin dissociation curve, which students learn in physiology. This curve plots the oxygen saturation (in %) on the vertical axis and pO2 on the

horizontal access. The oxygen saturation % steadily increases as the pO2 increases up to about a pO2 nearing 90 to 100 mmHg at which point the oxygen saturation is 99% to 100% (i.e., all the hemoglobin oxygen binding sites contain oxygen). If the patient breathes supplemental oxygen, the inspired pO2 increases to 200 mmHg, 400 mmHg or higher depending on how much oxygen is inhaled. Thus, a patient breathing supplemental oxygen may have a pO2 as high as 400 mmHg, but his oxygen saturation is still 100% (it can't get any higher than this). So the typical appearance of an oxygen hemoglobin dissociation curve, has a steep rise at pO2s below 100 mmHg, at which point it becomes a plateau since the oxygen saturation cannot increase above 100%.

Oxygen saturation can be measured continuously and non-invasively by pulse oximetry. Pulse oximetry uses light absorption through a pulsing capillary bed usually in a toe or finger, but it will also pick up in the nose, ear, palm, side of the foot, etc. The probe looks red, but it actually uses two light sources; one is red and the other is invisible infrared. Absorption using these two wave lengths measures oxygen saturation for hemoglobin A. Pulse oximetry will not measure the oxygen saturation correctly for other hemoglobins such as methemoglobin or carboxyhemoglobin. However, for sickle hemoglobin or fetal hemoglobin, the measurement is nearly as accurate as for hemoglobin A. Oxygen saturation can be measured by co-oximetry but this requires a blood sample Co-oximetry is capable of determining the true oxygen saturation for methemoglobin and carboxyhemoglobin. If the true oxygen saturation is known, then the pO2 can be estimated or calculated using the oxygen hemoglobin dissociation curve assuming that the patient is circulating hemoglobin A (which is not always the case).

The oxygen content is determined by the oxygen saturation percentage and the hemoglobin concentration. A patient with a hemoglobin of 14 has twice as much oxygen per ml of blood compared to a patient with a hemoglobin of 7, assuming that they both have 100% oxygen saturations. Similarly, the visual presence of cyanosis is dependent upon the concentration of desaturated (blue) hemoglobin. Thus, a patient with a hemoglobin of 7 at 80% saturation has a deoxygenated hemoglobin concentration of 1.4. This patient will visually appear to be just as blue (though paler) as a patient with a hemoglobin of 14 at 90% saturation, since this latter person also has a deoxygenated hemoglobin concentration of 1.4. Additionally, a patient with a hemoglobin of 14 at 80% saturation will look more cyanotic than a patient with a hemoglobin of 7 at 80% saturation. In this comparison, the more cyanotic patient is doing better with a higher oxygen content and oxygen delivery.

The hematocrit is the percentage of the blood that contains RBCs. The hematocrit is directly proportional to the hemoglobin concentration. The hematocrit (in percent) is roughly three times the hemoglobin concentration (in gm per dl). Chronically hypoxic patients can survive by raising their hematocrit as a compensation maneuver. Chronic hypoxia stimulates erythropoietin which stimulates RBC production raising the hematocrit. Thus, a patient with a normal hemoglobin of 12 (hematocrit 36) and an oxygen saturation of 100%, has the same oxygen content as a patient with an oxygen saturation of 80% and a hemoglobin of 15 (hematocrit 45). The former patient looks pink, while the latter patient looks blue.

The last factor is the oxygen delivery rate. This is determined by the oxygen content and the cardiac output. Conceptually, imagine a patient with a weak heart and only half the cardiac output of a normal patient with signs of congestive heart failure. If pulmonary edema were not present, and such a patient had an oxygen saturation of 100%, their hemoglobin would have to be twice as high as another patient with a normal cardiac output to achieve the same oxygen delivery rate. This might be better understood by measuring a patient's venous blood gas. In room air, a normal arterial pO2 would be 100 mmHg, and the venous pO2 would be about 75 mmHg. However, if a patient had a very low cardiac output, the arterial pO2 might still be 100 mmHg, but the venous pO2 might be 50 mmHg. This occurs because the cardiac output is so low, that much more oxygen is extracted from the RBCs as they pass through the capillaries.

Pulse oximetry can be fooled by conditions with abnormal hemoglobin color. The major condition in this category is carbon monoxide (CO) poisoning. CO poisoning results in the formation of carboxyhemoglobin. Carboxyhemoglobin does not carry oxygen. It is really a hemoglobin molecule with all oxygen carrying sites occupied by CO. The CO has such a high affinity for hemoglobin, that oxygen cannot displace it. Consider carboxyhemoglobin totally useless in oxygen transport. CO poisoning results from CO exposure, most commonly exposure to fuel combustion (fuel burning heaters, stoves, automobile exhaust, etc.), so it most commonly occurs during cold periods where people are in closed quarters to conserve the heat originating from fuel combustion. Symptoms include headache, nausea, vomiting and weakness. The patient is classically described as cherry red, but in reality, they appear to be pink, which lowers the clinician's suspicion for hypoxia. Thus, these symptoms are commonly attributed to viral flu-like illnesses. If a patient has a carboxyhemoglobin level of 25%, and their hemoglobin is 12, this means that they effectively have a hemoglobin of only 9 (since 25% of their hemoglobin is useless). If the carboxyhemoglobin level is 25%, then the maximum oxygen saturation that can be attained is 75%. However, the pulse oximeter will read 100% because the color of carboxyhemoglobin is bright red, which is what the pulse oximeter reads. Thus, pulse oximetry measurements are fooled by CO poisoning. The arterial blood gas is not usually helpful either. Since the ABG measures oxygen gas tension (pO2) and not oxygen content or true oxygen saturation, the oxygen gas tension (pO2) will be normal. The only abnormality on an ABG may be metabolic acidosis, which is a consequence of inadequate oxygen delivery to the peripheral tissues, resulting an anaerobic metabolism and lactic acid production. If CO poisoning is suspected, one must order a CO level or a test called co-oximetry. Co-oximetry is done routinely in some blood gas analyzers, but most do not, so this must be specifically ordered. Co-oximetry is capable of measuring the true oxygen saturation percentage and the percentage of nonfunctional hemoglobins such as carboxyhemoglobin and methemoglobin. The treatment for CO poisoning is oxygen, but if the CO level is very high, or if the victim is pregnant, hyperbaric oxygen is indicated to more effectively displace the CO from the hemoglobin.

Similarly, methemoglobinemia is a condition in which there are high circulating levels of methemoglobin which does not carry oxygen. The major difference is that methemoglobin is brown in color. Patients with methemoglobinemia are classically "ashen gray" in color. Their pulse oximetry value will read LOW, so this condition does not fool the pulse oximeter as it does in CO poisoning. Another clue is that when supplemental oxygen is given to the patient, the pulse oximetry reading does not change. It will still be low. When an arterial blood gas is drawn, the blood appears to be a chocolate brown color which is quite eye opening. A simple bedside test can be done by taking a drop of the patient's blood on a filter paper or gauze. Get another drop of blood from a normal person (either your or your fellow residents and medical students). Blow oxygen over the surface of these two blood spots. The normal blood will become red or stay red, while the methemoglobinemia patient's blood will stay the same color (brown or dark) since the methemoglobin will not carry oxygen. This illustrates the fact that the oxygen gas tension (pO2) does not reflect the degree of oxygen carrying capacity. Co-oximetry or a methemoglobin level can be ordered to measure the severity of the methemoglobinemia, but the pulse oximeter will be able to estimate it also. Most symptomatic methemoglobinemia occurs in infants with diarrhea. The cause is usually idiopathic, but the ingestion of nitrites is one of the known causes. The condition is usually self-limited and resolves gradually with IV fluid hydration. IV methylene blue can be given for severe cases. Oxygen supplementation is somewhat helpful and PRBC transfusion can be used to increase the oxygen carrying capacity in severe cases.

The two common elements of CO poisoning and methemoglobinemia is that the pO2 does not identify the condition. You can think of carboxyhemoglobin and methemoglobin as useless hemoglobin, just like the coffee in the cup example. Coffee (or water) is capable of carrying oxygen, but very little. Just because the pO2 of the coffee or carboxyhemoglobin or methemoglobin is 150 Torr, this does not mean that it is carrying much oxygen at all. CO poisoning is a harder diagnosis to make, because the pulse oximeter reads falsely normal. A typical ABG in CO poisoning or methemoglobinemia patients is pH 7.26, pCO2 34, pO2 100, bicarb 15, BE -11, if the patient is breathing room air. If the patient is breathing supplemental oxygen, then the ABG will be pH 7.26, pCO2 34, pO2 400, bicarb 15, BE -11 (i.e., just the pO2 goes up), although this does not change the oxygen saturation much. Although the blood gas machine will calculate that the oxygen saturation is 100%, remember that the ABG machine did not measure this, but rather it calculates this based on the assumption that the sample contains normal hemoglobin (which is not the case if the patient has CO poisoning or methemoglobinemia). The paradox is that the ABG slip will indicate that the oxygen saturation is 100%, while the co-oximetry report will indicate that the oxygen saturation is very low (e.g., 70%).

In summary, CO poisoning has a low true oxygen saturation, red color, 100% oxygen saturation on pulse oximetry (which is false), and normal pO2 on ABG. Methemoglobinemia has a low true oxygen saturation, brown color, low oxygen saturation on pulse oximetry, and normal pO2 on ABG.

Questions

1. Which patient has a higher oxygen content? Patient A with a pO2 of 100 or patient B with a pO2 of 70?
2. ABG pH 7.31, pCO2 60, pO2 80, bicarb 30, BE +4. What is the best description for this ABG considering the concepts of metabolic or respiratory acidosis or alkalosis, and metabolic or respiratory compensation?
3. Describe a possible clinical situation which would yield the ABG in question number 2 above?
4. At what pO2 or oxygen saturation does cyanosis become visible?
5. Write an example of an ABG in a patient with moderately severe diabetic ketoacidosis.
6. In a cardiac arrest victim, you get an ABG which shows pH 6.72, pCO2 55, pO2 200, bicarb 7, BE -25. What can you do to reverse the acidosis?
7. Well oxygenated patients are pink and poorly oxygenated patients are cyanotic. Is there a stage in between these? What is the color of these patients if they aren't pink and they aren't cyanotic? The answer to this question is not found in the above chapter.
8. What condition would give you the following results in an ill appearing patient breathing supplemental oxygen: Pulse oximeter reading 100%, pO2 on ABG 350 Torr, co-oximetry (true oxygen saturation) 65%.

References

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Answers to questions

1. This cannot be determined without knowing the hemoglobin or hematocrit of each patient. Patient A could paradoxically have a lower oxygen content if he has a substantially lower hemoglobin (severely anemic) than patient B.
2. This is a respiratory acidosis with metabolic compensation.
3. This patient has bronchopulmonary dysplasia (chronic lung disease) with chronic CO2 retention and metabolic compensation. An alternative answer would be an adult with chronic emphysema. An incorrect answer is acute respiratory failure, because if the respiratory failure were acute, the patient would not have enough time for metabolic compensation and his bicarb would be 24 or lower.
4. Visible cyanosis requires a certain amount of deoxygenated hemoglobin which is why the answer to this question depends on the hemoglobin or hematocrit. Patients with low hematocrits require a lower pO2 for visible cyanosis compared to patients which higher hematocrits. So there is no single answer to this question. For example, a patient with cyanotic congenital heart disease may have a high hemoglobin to compensate. If his chronic oxygen saturation is 80%, he can compensate by having a higher hemoglobin such as a hemoglobin of 16. He will be visibly cyanotic because 20% (100% minus 80% oxygen saturation) of his 16 hemoglobin is desaturated (i.e., 3.2 Hgb is desaturated). For a normal child with a hemoglobin of 13 to have 3.2 desaturated Hgb, this child would have to have 25% (3.2 divided by 13) desaturation (i.e., an oxygen saturation of 75%). Thus, one patient may look bluer at 80% saturation, while another would less blue at 80% because of different hemoglobins.
5. The pH should be low. The bicarb should be low (metabolic acidosis). There should be some respiratory compensation so the pCO2 should be low (hyperventilation or Kussmaul respirations). The pO2 should be fairly normal. So an example might be pH 7.14, pCO2 30, pO2 100, bicarb 10, BE -17.
6. This is a cardiac arrest so the patient is probably intubated. The high pCO2 indicates that the patient is being hypoventilated or the endotracheal tube is not in the trachea. Proper placement of the endotracheal tube should be confirmed. The tidal volume and respiratory rate need to be increased to increase the minute ventilation to decrease the pCO2. Better chest compressions to improve pulmonary blood flow will also facilitate the removal of CO2. The bicarb is low causing a metabolic acidosis. Sodium bicarbonate can be given intravenously to reverse the metabolic acidosis.
7. Their color is pale. Thus pallor can suggest anemia, poor skin perfusion or hypoxia.
8. CO poisoning.

Chapter VIII.2. Asthma
Franklin Y. Yamamoto, MD

A three year old comes in with a complaint of coughing for 2 weeks. Coughing is present every night. He has also had a mild fever, but his temperature has not been measured at home. His parents have been using a decongestant/antihistamine syrup and albuterol syrup which were left over from a sibling. Initially the cough improved but it worsened over the next 2 days. He is noted to have morning sneezing and nasal congestion. There are colds going around the pre-school. He has had similar episodes in the past, but this episode is worse. He has no known allergies to foods or medications.

His past history is notable for eczema and dry skin since infancy. He is otherwise healthy and he is fully immunized. His family history is notable for a brother who has asthma. In his home environment, there are no smokers or pets.

Exam: VS T 38.1, P 100, RR 24, BP 85/65, oxygen saturation 99% in room air. He is alert and cooperative in minimal distress if any. His eyes are clear, nasal mucosa is boggy with clear discharge, and his pharynx has moderate lymphoid hypertrophy. He has multiple small lymph nodes palpable in his upper neck. His chest has an increased AP diameter and it is tympanitic (hyperresonant) to percussion. Rhonchi and occasional wheezes are heard on auscultation, but there are no retractions. Heart is in a regular rhythm and no murmurs are heard. His skin is dry, but not flaky, inflamed or thickened.

He is initially felt to have moderately persistent asthma and possible asthmatic bronchitis. He is initially treated with nebulized albuterol and nebulized corticosteroids for bronchospasm and bronchial inflammation. He is also treated with an antihistamine at night to reduce his morning allergy symptoms. In follow-up, his cough does not improve and he is still having fever (T 38.2C, 101.0F). A chest X-ray is obtained, but no radiographic evidence of pneumonia is present. His cough persists, but only with exercise and drinking cold juice.

His chest now sounds clear in the office. After one week of no night cough, his nebulized albuterol+corticosteroid is reduced to 2 times a day. His exercise induced cough gradually resolves. His nebulized corticosteroid is replaced with nebulized cromolyn twice a day and oral montelukast (a leukotriene inhibitor) is added. He enrolls in a soccer league and plays with minimal coughing. His routine nebulized albuterol+cromolyn is stopped and is used only pre-exercise to prevent exercise induced bronchospasm. No cough is observed at night or with exercise. He is continued on nightly antihistamines, pre-exercise albuterol+cromolyn nebs, and once daily montelukast. He is given an asthma treatment plan which gives his parents clear instructions on which medications to start based on his symptoms and severity.

Asthma is by far, the most frequent respiratory diagnosis for children admitted to hospitals. It causes 5000 deaths annually in the United States despite the availability of excellent medications. Historically, asthma was characterized as a psychological illness, a surgical illness treated by removal of the carotid body, an environmental illness aggravated by air pollution, and an allergic illness or infectious illness. An allergy role in asthma, was legitimized by the discovery of IgE in 1965. Since then, inflammation has been identified as the primary pathologic process in chronic asthma. Because of the variety of asthma triggers, such as exercise, exposure to smoke, weather changes, and allergies, asthma is now considered to be a syndrome consisting of bronchospasm, airway hyperirritability, and inflammation. The popular term ROAD (reversible obstructed airways disease) or RAD (reversible airway disease) is not entirely accurate since this is only part of the disease process and reversibility may not always be evident. This is because obstruction of the airways may be secondary to mucous plugging or inflammatory changes decreasing the caliber of the airways, in which case, beta-2 bronchodilators are ineffective.

Currently the NIH Guidelines (1) have served as a standard for diagnosing and treating asthma. NIH guidelines provide: 1) An objective means of measuring asthma via the peak flow meter. 2) A way of objectively categorizing severity classes of patients based on symptoms and/or peak flow measurements. 3) A comprehensive pharmacologic plan primarily designed to treat inflammation, inclusive of provisions for acute and maintenance care, for each severity level. 4) For the identification and removal of (or control of exposure to) known triggers. 5) The direction for forming a partnership with the physician who uses education as a primary basis of this relationship.

The realization that IgE existed and could be found in allergic individuals propelled the field of allergy and understanding of asthma into a renaissance of elucidating the actual pathophysiology of allergic diseases. Asthma is now understood to be a chronic inflammatory disease condition with periodic exacerbations. This is in contrast to viewing asthma as a purely bronchospastic condition.

An acute asthma exacerbation is a biphasic process. Understanding the inflammatory process of asthma came about when it was observed that 4 to 8 hours following allergen exposure, wheezing would occur that was not responsive (or less responsive) to beta agonists but it was ablated by cromolyn and corticosteroids. However, beta agonists could easily neutralize the immediate reaction, occurring within minutes of the allergen exposure. This created a picture of a biphasic reaction to allergen (or infection) induced wheezing. The first phase was described as the immediate (bronchospastic) phase and the second phase as the late phase inflammatory response.

In the early phase of allergic inflammation, preformed mediators such as histamine and rapidly formed mediators such as leukotrienes are released and cause bronchospasm. Other mediators signal the late phase inflammatory cells. These cells (e.g., eosinophils) recruit other cells such as epithelial cells to participate in the resultant inflammatory damage of the airways and subepithelial structures. These events eventually result in extensive restructuring of the normal histology of the airways. This damage is not restored by beta-2 bronchodilators. An important immunologic occurrence is the activation of the Th2 helper cell, which is pivotal in the progression of the allergic immunologic process. The other helper designated Th1 cell does not enhance the allergic inflammatory process.

Asthma, whatever the severity, is a chronic inflammatory disorder of the airways. The characteristic features of asthmatic inflammation are: mast cell activation, inflammatory cell infiltration, eosinophils, macrophages, neutrophils (particularly in sudden-onset, fatal exacerbations), lymphocytes (TH2-like cells), edema, denudation and disruption of the bronchiolar epithelium, collagen deposition beneath the basement membrane (this is an irreversible process), goblet cell hyperplasia, mucous hypersecretion, and smooth muscle thickening. The primary clinical components of asthma include: bronchospasm, inflammation, airway hyper-reactivity, increased mucous production, and end expiratory hyperinflation ("air trapping").

There are many presentations of asthma. Asthma is present 24 hours a day, 7 days a week. It may not be in an easily identified form (i.e., there may be no obvious symptoms present). The most recognizable form is the acute episode in which the patient presents with acute shortness of breath. Depending on the underlying degree of inflammatory damage of the airways, the episode may have been festering with persistent cough and occasional bouts of shortness of breath for weeks. Failure to attend to these soft signs of "asthma in transition" may lead to an acute case of status asthmaticus. Hence, paying attention to signs of "silent asthma" (asthma not in an acute phase), can prevent costly and life threatening consequences. Asthma may appear solely as an event associated with work or exercise. Most asthma in childhood occurs as a result of encounters with respiratory viruses. If the asthmatic is already unstable because of a poor

maintenance regimen of the existing chronic asthma, the acute phase will begin simultaneously with the first signs of a "cold". If the asthma is managed well, then the cough and wheezing may occur several days after cold symptoms. Hence, early recognition of "asthma in transition" is a major point of cooperation involving the physician and patient. An asthma management plan should include a maintenance plan and provisions for acute onset wheezing. Asthma in its most manageable state, is outpatient asthma, as opposed to hospital status asthmaticus.

For most medical professionals, the first and everlasting impression of asthma is in hospital status asthmaticus. By far, the more common situation is asthma outside the hospital, in its non-acute form. Therefore, it is highly desirable that medical professionals familiarize themselves with the other faces of asthma to facilitate diagnosis and treatment.

The type of medication used to treat asthma reflects the mechanism of airway obstruction: bronchospasm versus inflammation. This is an extremely simplified version of what really goes on and new pieces of the intricate mechanism are being uncovered. However from a pragmatic standpoint, the logic for appropriate use of individual medications for asthma can be understood by recalling the biphasic reaction.

Based on this brief description of the mechanism of asthma, it is now possible to create an asthma treatment program. Genetics aside, elimination of triggers and aggravators of asthma such as allergens, cigarette smoke, and environmental and industrial pollutants, can prevent acute exacerbations of asthma and serve as the first line of defense. Conditions such as weather changes and respiratory infections fall outside of the readily controllable factors.

Approach to Asthma

1. Diagnose asthma and classify severity. Identify aggravating and triggering conditions.
2. Prepare an initial treatment plan to stabilize the acute condition. Instruct patient and parents on signs and symptoms which help to monitor the effectiveness of treatment. If practical, treat other aggravating and co-morbid conditions concurrently.
3. When asthma is stable, proceed to a maintenance plan to allow healing of the damaged airways. This may take weeks to months. Prepare an asthma action plan for up-regulation of medications for unexpected exacerbations.
4. When there are no signs of breakthrough cough or wheezing, indicating that the airway hyper-reactivity has subsided and is controlled, switch to a long term maintenance plan. This might be PRN use of bronchodilators, or pre-exercise use of preventive medications, or pulsing of medications for cold symptoms in short bursts.
5. Monitor asthma with periodic evaluations and reminder messages of avoidance and check on patients' inhalation technique of medication administration.

Inflammation in asthma contributes to: airway hyperresponsiveness, airflow limitation, respiratory symptoms, coughing, wheezing, shortness of breath, rapid breathing, chest tightness, persistent symptoms, and pathologic damage, even when symptoms are not present. It is often thought that periodic control of acute symptoms is sufficient, but this is suboptimal. Utilization of chronic anti-inflammatory agents result in better long term outcomes for all but the mildest asthmatics.

Co-morbid conditions such as allergic rhinitis, sinusitis, eczema, and gastroesophageal reflux have profound influence on asthma. Their presence makes asthma extremely difficult to control. The main goal is to keep the patient functional and free of side effects from medications. With this approach, asthmatics have been able to participate in a normal life style.

Asthma is more than an acute process. A large part of treating asthma successfully is to be able to recognize asthma in its early stages and to formulate an appropriate treatment plan before the asthma advances to a critical stage. It is simple to diagnose asthma when the patient is wheezing, displaying intercostal retractions and turning pale or blue. Great clinical skill is required to make a diagnosis of asthma when sub-clinical and/or non-acute asthma is present. A careful detailed history and physical exam are crucial to this end. Asthma is not the acute episode of wheezing as popularly described in lay journals and magazines, but a chronic condition of the airways of the lungs which exhibits recurrent bronchospasm. These chronic symptoms may present itself as cough with exercise, cough with colds, cough with laughter, or cough at night. A peak flow meter can consistently record airflow readings compared against normal values for sex and age.

Signs of "silent asthma" (when no wheezing is heard) include: persistent cough at night, cough with exercise, cough with laughter, cough when consuming cold foods or drinks, prolonged cough following or accompanying a cold, feeling of "tight chest" or difficulty breathing.

The peak flow measurement and FEV1 (forced expiratory volume over one second) are effort dependent measures. Full pulmonary function testing is desirable; however, the equipment is expensive compared to an inexpensive peak flow meter. The ultimate objective measurement for asthma is by body plethysmography (body box), which can measure the end expiratory residual lung volume as well as resistance to airflow. For those patients unable to perform peak flow measurements, clinical history is all you may have to base your conclusions. This includes a major group of younger asthmatics from infancy to 4 or 5 years old. Many children in this age group are unable to reliably perform peak flow measurements.

Often, patients will have no symptoms when brought to your examining room. The identification of the role of allergic diseases in asthma relies heavily on patient history. Physicians trained to respond to record what they feel, see, and hear may have a problem forming conclusions based on history alone. Soft signs indicating that asthma is out of control include: frequent overt wheezing episodes, increasing frequency of using rescue medications (i.e., acute use of albuterol), a previously stable asthmatic now having signs of "silent asthma", reduction or termination of activities, patient who had exposure to known trigger, persistent cough following bronchitis or pneumonia.

The National Institutes of Health (NIH) guidelines, list as one of several key objectives, forming a partnership with the patient to facilitate treatment of asthma. Good communication and availability to answer questions and concerns are basic to the partnership. Part of your efforts as the treating physician should be focused on getting the patient to respond in a logical manner to cope with changes in his/her clinical state. This is based on the patient understanding the principles of: triggers and aggravators, bronchodilation, inflammation, airway hyper-reactivity and healing. Patients must also understand mucous mobilization and signs and symptoms of asthma out of control which may lead to an acute asthma attack. For example, should the peak flow fall or cough increase, the patient is instructed to upgrade their medications according to a prearranged plan. As the acuteness of the situation resolves, the patient is advised to downgrade their medications back to their maintenance program. Should there be an unanticipated episode of wheezing, immediate activation of the action plan and consultation with the physician for additional treatment schemes is the next step. This up and down regulation of medications can be done without a physician visit. Phone calls, informing the physician's office of these maneuvers, are all that is normally required. Obviously, recurrent wheezing episodes, even if reversed easily might indicate the presence of an unstable condition requiring an

adjustment in the basic asthma management plan. Hence, the physician should be apprised of these changing conditions regularly. All asthma management plans should have common goals.

Asthma management plans depend on the severity of the asthmatic. Higher severity levels warrant greater use of corticosteroids and prophylactic medications such as leukotriene inhibitors and inhaled corticosteroids. The NIH guidelines categorizes severity levels into "steps" as follows:

Step 1 (mild intermittent): Day symptoms two days per week or less and night symptoms two nights per month or less. Chronic peak flow is 80% of expected or higher.

Step 2 (mild persistent): Day symptoms greater than two times per week, but less than once per day or night symptoms greater than nights per month. Chronic peak flow is still 80% of expected or higher.

Step 3 (moderate persistent): Day symptoms occur daily or night symptoms occur more than once per week. Chronic peak flow is 60% to 80% of expected value.

Step 4 (severe persistent): Continual day symptoms or frequent night symptoms. Chronic peak flow is less than or equal to 60% of expected value.

The use of peak flow in the above classification is not required in children 5 years and under. Peak flow data is useful but not required for classification in older age groups, but most children in this age range are capable of performing peak flows.

The major goal is to allow the child to express and achieve his or her maximum natural potential by not allowing the asthma to control him or her. This is a good way to view the end point in asthma management. Along the way, it is crucial to cradle the impressionable self image so that the child does not have a negative view of himself or herself. The very impressionable years are from about 3 to 10 years of age, when children form their life-long mental image of themselves. Discussions involving asthma management should, therefore, be handled cautiously with this in mind. Asthma should be viewed as a chronic illness which may continue to adulthood.

Bronchodilators

In 1896 Solis-Cohen published, "The use of adrenal substances in the treatment of asthma" (adrenalin or epinephrine is a fast and potent bronchodilator). Epinephrine (most commonly administered subcutaneously, but it could be inhaled as well) was the first line of treatment for acute asthma from the 1950s through the 1970s and early 1980s.

In 1924 ephedrine was isolated from Ma Huang (a Chinese root extract). For the next forty years, ephedrine would be the mainstay for asthma treatment in the USA. Ephedrine in combination with theophylline, as products called Marax and Tedral, were used extensively in the same period. Interestingly, the ancient Chinese boiled the ephedra root in strong tea for their concoction to treat asthma. The tea contained theobromine, a methylxanthine. Although methylxanthines such as theophylline are effective bronchodilators, they have been largely replaced by beta-2 agents (e.g., albuterol) which have a faster onset and less toxicity. Adding theophylline does not appear to acutely benefit most patients who are receiving high therapeutic doses of albuterol. Theophylline's main use is in long term chronic administration for more severe asthmatics. This change in therapeutic approach from methylxanthines to beta-2 agents did not further our understanding of the true pathophysiology of asthma, as bronchodilation was the only target of treatment. Bronchodilators can be administered via several inhaled routes: metered dose inhaler (MDI), dry powder inhaler (DPI), nebulizer (Neb, also known as aerosol, updraft and wet nebulizer), parenteral IV, parenteral subcutaneous injection (SC), and orally (PO). In general, inhaled medications have a faster onset, greater potency and less side effects.

Bronchodilators Used in Asthma

A. Beta-2 Agonists:
   - albuterol (Ventolin, Proventil, also called salbutamol outside the USA) - MDI, Neb, PO
   - L-albuterol (Xopenex - active isomer only) - Neb
   - terbutaline - MDI, Neb, PO, SC
   - formoterol (Foradil - very long acting) - DPI
   - salmeterol (Serevent - used for maintenance therapy) - DPI, MDI
   - epinephrine (alpha and beta) - MDI, Neb, SC

B. Anticholinergics
   - ipratropium bromide (Atrovent) -MDI, Neb
   - oxitropium bromide (Oxivent) - MDI
   - atropine -Neb

C. Methylxanthines
   - aminophylline - PO, IV
   - theophylline - PO, IV
   - oxtriphylline - PO

Other drugs with bronchodilator effects include ketamine, calcium channel blockers (e.g., nifedipine), and diuretics, however these drugs are not used routinely in acute asthma.

Anti-Inflammatory Drugs

Based on the biphasic mechanism, an anti-inflammatory drug (i.e., corticosteroids) is necessary for the complete treatment of asthma. Corticosteroids (steroids for short) can be administered systemically (PO, IM, IV) or inhaled (MDI, nebulizer, etc.). For asthma of a chronic nature, such as allergic asthma to house dust, a daily regimen of a long acting bronchodilator coupled with a steroid by inhalation would be effective. Steroids take hours to become engaged in its active phase. Their action does not take place directly on the inflammatory tissue but by modulating DNA production of pro-inflammatory cytokines. Their effects are very broad and nonspecific. Steroids affect virtually every phase of the inflammatory process. They have an array of impressive and undesirable side-effects, which cause hesitation in their use by physicians as well as patients. As in the use of any medication or therapeutic agent, the employment of steroids is subject to weighing the desired effects against the undesirable effects (benefit vs. risk). If the positive effects of using steroids have an overwhelming advantage over not using the drug, then it is justified to be used on a regular basis. This especially applies to children where growth suppression (in the order of 0.5 to 1.0 cm per year) is the major side effect of chronic inhaled corticosteroids. Catch-up growth occurs in most instances, if the child's condition improves to the point at which inhaled corticosteroids are no longer

needed. Many patients require more medications during the fall/winter/spring, and fewer medications during the summer. Occasional bursts of systemic corticosteroids have no significant long term side effects, but chronic or long term use of systemic steroids have major side effects (refer to the chapter on corticosteroids).

Corticosteroids used in Asthma
- beclomethasone (Beclovent, Vanceril) - inhaled
- triamcinolone (Azmacort) - inhaled, IM
- budesonide (Pulmicort) - inhaled
- fluticasone (Flovent) - inhaled
- flunisolide (AeroBid) - inhaled
- mometasone (Asmanex) - inhaled
- prednisone - PO
- prednisolone (Pediapred, Prelone, Orapred) - PO
- methylprednisolone (Medrol, Solumedrol) - PO, IV
- dexamethasone (Decadron) - PO, IV

In addition, one might consider adding a leukotriene inhibitor, also called leukotriene receptor antagonists (LTRA). These leukotriene inhibitors were developed to counteract the all important late phase inflammatory reaction caused by SRS-A (slow reacting substance of anaphylaxis), a compound which was eventually identified as leukotrienes. Their side effects are minimal. These are all given orally.

Leukotriene receptor antagonists (LTRA)
- montelukast* (Singulair)
- zafirlukast* (Accolate)
- pranlukast
- zileuton (Zyflo)

*(Some sources spell the suffix as "leukast" instead of "lukast". Roche and Astra Zeneca spell it as "lukast".)

Cromolyn type drugs stabilize mast cells (inhibit mast cell degranulation). They have less potent anti-inflammatory properties, but they have minimal side effects. Cromolyn (Intal) is available via nebulizer and MDI. Nedocromil (Tilade) is available via MDI.

Goals of Asthma Treatment
1. Prevent chronic and troublesome symptoms (e.g., cough or breathlessness in the night, in the early morning, or after exertion).
2. Maintain (near) "normal" pulmonary function.
3. Maintain normal activity levels (including exercise and other physical activity).
4. Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations.
5. Provide optimal pharmacotherapy with minimal or no adverse effects.
6. Meet patients' and families' expectations of and satisfaction with asthma care.

Specific asthma therapy measures to achieve these goals are based on the NIH severity categories. Step 1 (mild intermittent) requires no daily medications. ALL of the other categories (i.e., any category with the word "persistent"), requires a chronic controller anti-inflammatory medication.

Step 2 (mild persistent) recommends a low dose inhaled corticosteroid. Alternatively, a cromolyn medication or a leukotriene receptor antagonist may be used. Theophylline is another option, but only in children older than 5 years.

Step 3 (moderate persistent) recommends a low dose inhaled corticosteroid plus a long acting beta-2 agonist (salmeterol or formoterol). Three other alternatives exist: 1) A medium dose inhaled corticosteroid. 2) A low dose inhaled corticosteroid plus an LTRA. 3) A low dose inhaled corticosteroid plus theophylline.

Step 4 (severe persistent) recommends a high dose inhaled corticosteroid, plus a long acting beta-2 agonist.

In addition to the above chronic (long-term) recommendations, acute exacerbations are treated with quick relief (or rescue) medications, which is most commonly prn albuterol and optional short bursts of systemic corticosteroids. Albuterol can be given: 1) Orally at 0.1 mg/kg per dose every 6 to 8 hours. 2) Via nebulizer 2.5 mg unit dose every 4-6 hours. 3) Via metered dose inhaler (MDI) 2-4 puffs every 4-6 hours (however, most studies suggest that 5 to 10 puffs is more equivalent to the 2.5 mg nebulizer treatment).

Systemic corticosteroids are commonly administered as: 1) Oral prednisolone at 2 mg/kg/day given once daily or divided BID. 2) IV methylprednisolone 2 mg/kg, then 1 mg/kg every 6 hours. Systemic corticosteroids are usually given for 4 to 5 days and then discontinued if the patient improves. Systemic corticosteroids administered for longer than 7 days require a gradual taper of the medication. If the patient is on inhaled corticosteroids, these should be resumed once systemic corticosteroids are stopped or tapered. Some physicians continue inhaled corticosteroids during systemic corticosteroid bursts to avoid the confusion caused by modifying their chronic medications.

All patients should have a written asthma management plan that describes their chronic medications and a plan for the initiation of a rescue plan based on their symptoms and peak flow (if age >5 years). More detailed plans can include recommendations to step up or step down their chronic medications as their chronic symptoms worsen or improve.

If dyspnea still persists, despite rescue medications, then the asthma management plan should refer the patient to a source of immediate medical care (doctor's office during office hours, or emergency room after hours). Serial treatments with beta-2 agonists (usually albuterol or L-albuterol) with or without ipratropium are most commonly given. Inhaled beta-2 agonists can be given continuously for severely ill patients, or serially based on severity. Systemic corticosteroids can be started. Parenteral corticosteroids do not have an onset time advantage over oral corticosteroids; however, very ill children have a higher likelihood of vomiting oral prednisolone. Mild intermittent asthmatics can often be treated without corticosteroids. The decision to start systemic corticosteroids is based on their response to beta-2 agonists and their previous history which indicates their severity level. Those who do not respond well to beta-2 agonists should be started on systemic corticosteroids because, poor response indicates the presence of significant bronchial

inflammation Those who have required systemic corticosteroids in the past or who have other markers of more severe asthma should also be started on systemic corticosteroids.

Characteristics of good asthma control in children include: no coughing, no shortness of breath or rapid breathing, no wheezing or chest tightness, no waking up at night because of asthma symptoms, normal activities including play, sports, and exercise, no episodes of asthma that require a doctor visit, emergency room visit, or urgent care, no absences from school or activities, no missed time from work for the parent or caregiver, normal or near normal lung function, and a healthy self image (i.e., "nothing can stop me attitude").

Unfortunately, the death rate from asthma is not yielding to the introduction of many excellent and powerful treatments. This condition remains a challenge to the medical care team at all levels from physicians, nurses, emergency technicians, and respiratory therapists to psychiatrists and social workers. Family, school personnel, coaches, club leaders, and after hours activity supervisors, are all involved in delivering care to the asthmatic.

Risk factors for death from asthma include:

Past history of sudden severe exacerbations.
Prior intubation for asthma.
Prior admission to intensive care unit for asthma.
Greater than 2 hospitalizations for asthma in the past 12 months.
Greater than 3 emergency room visits for asthma in past 12 months.
Hospitalization or emergency care visit for asthma in the past month.
Use of more than 1 canister per month of inhaled short-acting beta 2 agonist.
Current chronic use of oral corticosteroids.
Difficulty perceiving airflow obstruction or its severity.
Low socioeconomic status and urban residence.
Illicit (illegal) drug use.
Serious psychosocial problems.

Acute signs of severe asthma and potential impending respiratory failure, warranting admission to an intensive care unit include: 1) Oxygen saturation less than 100% despite the administration of supplemental oxygen. 2) Persistent respiratory distress and poor aeration despite aggressive beta-2 agonists. 3) A pCO2 of 40 or greater on a blood gas. The treatment of severe status asthmaticus bordering on respiratory failure is controversial. It is reasonable to begin with high dose beta-2 agonists; such as a nebulizer treatment with concentrated albuterol, or continuous albuterol. In severe patients, aeration is poor, so inhaling albuterol by itself is usually insufficient. Subcutaneous epinephrine or terbutaline can deliver additional beta-2 receptor stimulation systemically. Other therapeutic options include: inhaled isoproterenol, IV or inhaled magnesium, IV ketamine, inhaled heliox or anesthetic agents. Such patients should be treated aggressively from the onset to prevent respiratory failure. If the patient fails to improve and respiratory failure ensues, positive pressure ventilation should be directed at maintaining oxygenation above 90% saturation if possible. Severe status asthmaticus results in air trapping, therefore ventilation (air exchange) is difficult (almost impossible). Although such patients have very high pCO2s because of air trapping and poor ventilation, the priority should focus on maintaining oxygenation. Attempting to normalize the pCO2 with aggressive positive pressure ventilation will increase the likelihood of a pneumothorax which will worsen the hypoxia. This strategy is known as "permissive hypercapnia" because hypercapnia is not as deadly as hypoxemia. Permissive hypercapnia is more likely to avoid a pneumothorax and thus, oxygenation is preserved, improving the overall outcome.

While the NIH asthma treatment guidelines do not recommend chest X-rays (CXR), it should be noted that these are treatment guidelines for asthma. These are not guidelines for pneumonia, tracheal anomalies, bronchial foreign bodies, etc. Thus, the CXR may be necessary in the process of evaluating some patients to be certain that the patient has asthma and NOT some other condition which can only be identified on CXR (i.e., to rule out other conditions).

Environmental measures to reduce asthma severity focuses on elimination of household smoking and the reduction of exposure to dust mite and cockroach microantigens in the environment. Wrapping mattresses with plastic casings, conversion of carpeted floors to tile floors, replacing drapes with blinds, and selecting home furnishings which avoid antigen accumulation, may result in improvement. Allergy testing and subsequent immunotherapy to desensitize a patient may be beneficial in some asthmatics.

In summary, asthma is a condition of multiple factors. It can be looked upon as a syndrome of multiple but related elements. It is basically a chronic condition with biphasic components which both result in airflow obstruction by different means. The treatment should take into account the various triggering factors, occupation, age, psychosocial, and economic factors.

Questions

1. How can you best describe asthma?
2. Can you describe the various medications to treat asthma?
3. Can you describe the parameters that are used to classify severity of asthma?
4. Describe clinical findings signifying the severity of an acute asthma exacerbation.
5. Discuss the approach to an asthmatic in relationship to formulating an acute asthma treatment plan. What questions do you ask, what physical findings do you look for, and what laboratory parameters are measured?
6. Formulate an asthma maintenance plan.
7. Describe various triggering factors and mechanisms by which they might exert their action.
8. Describe the immunologic chain of events that ultimately leads to bronchospasm and inflammation.
9. Discuss the pros and cons of corticosteroid use in children and compare them with use in adults.
10. How would you convince parents of asthmatics to use medications when their children are not openly symptomatic?

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Answers to questions

1. Asthma is best thought of as a chronic inflammatory condition consisting of obstruction of the airways of the lung caused by spasms of the smooth muscle surrounding the airways which, in some cases, can be easily reversed by beta adrenergic bronchodilators. In other cases, corticosteroids may be necessary to reverse the airway obstruction by reducing the inflammatory changes responsible for the airway narrowing. These changes may be caused by a variety of different stimuli.

2. Medications are divided into groups directed towards relaxing bronchial smooth muscles (relievers) and reversing the inflammation (controllers).

3. This answer can be divided into two parts. The first is used to describe the degree of severity of the acute asthmatic episode. These would include rate and effort of respirations, ability to move air through a peak flow meter or spirometer, and oxygen and carbon dioxide concentration in the arterial blood. The second parameter involves the sensitivity of the airways (i.e., the chronic severity classification described in the chapter). Day symptoms, night coughing episodes, peak flow, coughing with exercise, prolonged coughing after upper respiratory infections, and coughing with drinking ice-cold beverages help to categorize the severity of asthma.

4. Wheezing may be heard but if the attack is very severe there may be no wheezing at all (due to poor air exchange). Aeration is a good indicator of acute severity. Evidence of respiratory distress (retractions, tachypnea) indicates increasing severity until respiratory failure occurs (at which point, the patient may tire and exhibit seemingly less respiratory distress). Hypoxemia is also indicative of severity. Peak flow is typically low for acute exacerbations. For mild cases, cough may be present at any phase of an asthmatic episode and may be the only sign that bronchospasm is occurring. A peak flow meter reading before and after a challenge of inhaled bronchodilator may reveal an increase in the airflow indicating the presence of bronchospasm.

5. Always consider the triggering event in formulating the treatment plan. Avoidance of the trigger can be very cost effective. Preventive use of medications can be very useful such as preemptive use of medication with first sign of a cold. Analysis of the symptom's response to initial treatment can guide you in up regulating or down regulating medications. Use of the peak flow meter can serve as an objective means of adjusting medications. If cough and wheezing occur often and there are signs/symptoms of chronic asthma, a maintenance plan of daily medication should be initiated. Efforts should be made to approximate the degree of inflammation in the airways. This estimation can serve to guide you in the type and dosage of anti-inflammatory medications to use. A contingency plan of what medications to use during an acute episode can be helpful and may help to avoid an unnecessary emergency visit to the hospital.

6. The asthma maintenance plans are dependent on the patient's severity class (step 1, 2, 3, or 4). For all "persistent" levels, a daily plan will usually involve a long-acting bronchodilator and corticosteroid, LTRA, cromolyn and/or theophylline two to three times a day. Regular monitoring with peak flow meter readings can help to determine if the treatment is helping to return the lungs to normal function. A "rescue" plan using short acting bronchodilators with optional systemic corticosteroids may be needed for breakthrough wheezing.

7. Allergen exposure is mediated through IgE with resultant immediate and late phase reactions. A variety of mediators are released and cause a cascade of immunologic events culminating in tissue edema, increased mucous production, and sloughing of the epithelial layer of the inner lining of the airways. This affects the free and easy movement of air to the alveoli, which affects air exchange and causes atelectasis as the smaller air ways are completely plugged by the thickened mucous.

8. Triggering mast cells cause release of mediators, which can cause immediate effects on the lung tissue and smooth muscles. Other mediators are formed and released later and serve primarily to attract inflammatory cells. Some of these late mediators help to capture the incoming cells. Other mediators recruit epithelial cells and transform then into participants of the reaction causing them to release more mediators (biologic amplification).

9. The critical issue of steroids in children is that of linear growth. It is now well established that the use of inhaled steroids has significantly less effect on growth than systemic corticosteroids. The length of steroid use (inhaled or systemic), may have some effect on growth but its effect is temporary and in many studies final growth of asthmatics is generally no different than in non asthmatics (i.e., catch up growth occurs if the corticosteroids can be stopped for a period of time long enough for this to occur). Chronic inflammatory suppression (long term use of inhaled corticosteroids) improves the long term outcome of asthma (i.e., less severity in the future).

10. This is where your ability to practice medicine is tested. You need to educate and persuade the parents that your recommendations are in the best interest of their child and that it is based on considering the risks against the benefits. This is ideally done without making the parents feel guilty or intimidated by the potential for fatal outcomes. While our goal may be to maintain the patient's lifestyle and lung function, patients may see their goal as getting off medications as soon as possible. For persistent asthmatics, they should be convinced that this is a chronic disease and long term medications will be required. Long term use of medications is generally very safe and not addictive.

Chapter VIII.3. Cystic Fibrosis
Wallace J. Matthews, Jr., MD

"The child who tastes salty will soon die" -- German folklore

An 8 month old child presents with a history of poor growth and a chronic cough. He was the product of a 21 year old Gravida 2 Para 1, Ab 0 mother and was born at 41 weeks of gestational age. Soon after birth, he developed respiratory distress and was admitted to the neonatal intensive care unit where he was mechanically ventilated for 1 day and discharged after 5 days. He was initially breast-fed, but due to frequent vomiting and loose bowel movements, he was changed to formula feeding. Despite trials of different types of formulas (soy, hypoallergenic, etc.), his clinical course was remarkable for bloating, diarrhea and failure to thrive. He developed a daily cough and some respiratory difficulty. At the age of 5 months he was hospitalized for respiratory distress and was diagnosed as having asthma. He continued to have loose, large, greasy, foul-smelling stools and failure to thrive. An iontophoresis of pilocarpine sweat test is now being obtained.

Family history: Mother (age 21), racially mixed Japanese, Chinese, English and Irish. Father (age 23), racially mixed, Portuguese. Hawaiian and Chinese. He has a sister (age 2). All three family members are alive and well.

Exam: VS T. 37.0 C. P120, R45, BP 80/60, oxygen saturation 97% in room air, weight 6.7 kg (<5th percentile). He is alert and active in no distress. He is small for his age. HEENT exam is significant for bilateral otitis media and mild nasal congestion. Neck supple without adenopathy. Heart regular. Lungs with good aeration and mild wheezing and rales. Abdomen soft, non-tender, active bowel sounds. Color and perfusion are good.

Chest radiographs: Some hyperexpansion with increased peribronchial markings.

Laboratory Results: Sweat test: Weight 120 micrograms; 105 mmol/L (normal <60). Deep throat culture after coughing induced by respiratory therapy using a suction trap collection unit (specimen treated by laboratory as a sputum culture): Klebsiella pneumoniae. AST 44 H (normal 0-37), ALT 49 H, (normal l0-40), Alk Phos 324 (normal 104-345). Cystic fibrosis mutation analysis (genetic testing): Positive for one copy of Delta F508 and one copy of R1066C.

A series of events that took place during the very hot summer of 1938 in New York City led to the recognition of a new disease, cystic fibrosis. Dr. Dorothea Anderson (1) noted that a number of children presented to Columbia Hospital with severe dehydration, but without diarrhea or vomiting. Several of these children had been followed in the GI clinic for failure to thrive and greasy stools. Many also coughed. Thus began the recognition of cystic fibrosis of the pancreas (CF). By 1946, the genetic nature of this autosomal recessive disease was described. In 1953, Dr. Paul di Sant'Agnese recognized that CF patients lost excessive salt in their sweat (2), forming the basis for use of the sweat chloride test as a cornerstone of the diagnosis of this disease. The chloride values for patients with cystic fibrosis were elevated and a clear separation from normal volumes was found to exist. Similar elevations for sodium as well as potassium exist but there is greater overlap with the normal population. Historically, obtaining a sweat test involved bundling the child to induce sweating. Sometimes children were even placed near furnaces to make them sweat more profusely. This resulted in some deaths. Informed consent for testing was not obtained in those days. Currently, the iontophoresis of pilocarpine (a cholinergic agent) is used to induce sweating (3). This is a safer and standardized method of obtaining a sweat sample for the sweat chloride test. Some causes of a false positive sweat test include conditions associated with serum electrolyte abnormalities or conditions associated with abnormal skin and sweating. These include adrenal insufficiency, anorexia nervosa, atopic dermatitis, ectodermal dysplasia, fucosidosis, mucopolysaccharidosis type 1, and nephrogenic diabetes insipidus among others. A positive sweat test in association with pancreatic exocrine dysfunction (maldigestion as opposed to malabsorption) and lung disease is the diagnostic triad of CF.

Cystic fibrosis is said to be the most common, lethal inherited disease of white people. Cystic fibrosis occurs in 1:2,500 whites in North America, 1:8,000 Latinos (4), 1:17,000 African-Americans (5) and 1:32,000 Asian-Americans (6). Since the life expectancy of patients with CF has increased to more than 30 years, some have called it a semi-lethal disease. A better term would be a disease associated with a dramatically decreased life expectancy.

The CF mutation (7) has been localized to chromosome 7, band q31 (8). This locus codes for a transport protein named the cystic fibrosis transmembrane conductance regulator (CFTR) (9). More than 800 mutations are now known. The Caucasian associated delta F508 defect is the most common mutation found. The R1066C identified in this child is one of the rarer CF genes. It is found in people of Portuguese decent. The CFTR protein functions as a chloride channel regulated by a cAMP dependent protein kinase phosphorylation. The genetic variations and molecular implications are becoming clearer (10). The clinical features associated with cystic fibrosis are listed in the table below:

Phenotypic Features Consistent With The Diagnosis of Cystic Fibrosis (11)

1. Chronic sinopulmonary disease manifested by:
   a. Persistent colonization/infection with typical CF pathogens including: Staphylococcus aureus, non-typable Haemophilus influenza, Pseudomonas aeruginosa, mucoid and non-mucoid, Burkholderia cepacia, E. coli mucoid type (12), other gram negative organisms.
   b. Chronic cough and sputum production.
   c. Persistent chest radiograph abnormalities (e.g. bronchiectasis, atelectasis, infiltrates, hyperinflation, peribronchial cuffing).
   d. Airway obstruction manifested by wheezing and air trapping.
   e. Nasal polyps: radiograph or CT abnormalities of the paranasal sinuses.
   f. Digital clubbing.
2. Gastrointestinal and nutritional abnormalities including
   a. Intestinal: meconium ileus, distal intestinal obstruction syndrome, rectal prolapse.
   b. Pancreatic: pancreatic insufficiency; recurrent pancreatitis, diabetes mellitus.
   c. Hepatic: chronic hepatic disease manifested by clinical, biochemical or histologic evidence of focal biliary cirrhosis or multilobar cirrhosis.
   d. Nutritional: failure to thrive (protein-calorie malnutrition), hypoproteinemia and edema; complications secondary to fat soluble vitamin deficiency.

3. Salt loss syndromes (acute salt depletion; hypochloremic metabolic alkalosis).
4. Male urogenital abnormalities resulting in obstructive azoospermia.

In a review of cystic fibrosis patients, the frequency of presenting signs and symptoms were: acute and persistent respiratory illnesses (51%), failure to thrive or malnutrition (43%), abnormal stool or steatorrhea (35%), meconium ileus or intestinal obstruction (19%), family history of CF (17%), electrolyte imbalance (5%), rectal prolapse (3%), nasal polyps/sinus disease (2%), hepatobiliary disease (1%), and prenatal diagnosis by chorionic villus sampling or amniocentesis (1%) (13). Almost all male CF male patients have azoospermia due to occlusion of the tubules in the testes. Adult men have been diagnosed with cystic fibrosis after being evaluated for infertility (no sperm found in their semen sample).

Gastrointestinal complications are the most obvious early presenting symptoms. Approximately 19% of babies with CF present with meconium ileus, an intestinal occlusion in neonates which results from thick, viscid meconium obstructing the small bowel. This frequently results in a distal microcolon that requires surgical intervention. Others present with rectal prolapse in association with failure to thrive. As in the case presented above, fat maldigestion, steatorrhea and failure to thrive are presenting features. Some degree of pancreatic enzyme deficiency is found in 80-90% of CF patients. It is important to note that 10-20% of CF patients do not have this component of the disease and its absence does not preclude the diagnosis of CF. Pancreatic replacement enzymes, dietary regulation and the replacement of the fat-soluble vitamins (ADEK) play a major role in treating these GI complications. Since better enzymatic preparations are now available, fat restrictive diets are rarely needed. Once this therapy begins, patients grow rapidly, with catch up growth and normal subsequent growth percentiles. Further growth failure is usually related to pulmonary disease and its complications, listed below. Hepatic involvement is usually limited to hepatic enzyme elevations as was seen in our case. This can progress over time to frank hepatic disease and cirrhosis. Blood flow can be diverted from the liver which results in esophageal varices which can present with bloody vomiting (hematemesis).

As CF patients get older, pancreatic complications include pancreatitis as well as the insulin deficient form of diabetes mellitus. This diabetes mellitus is rarely associated with ketoacidosis. In spite of this, insulin therapy is required to treat the caloric losses associated with this complication.

It soon becomes apparent, however, that the pulmonary aspects of this disease are the major, life-limiting process. It progresses from a bronchiolitic process with chronic bacterial colonization of the airway, to bronchiectasis and obstructive pulmonary disease. In infancy, the organisms are most frequently Staphylococcus aureus, non-typable Haemophilus influenza, and other gram negative organisms (14). These are often replaced by Pseudomonas aeruginosa (both mucoid and non-mucoid colony type). Once established in the airways, mucoid pseudomonas is almost impossible to eradicate. There seems to be a local environment in the CF airways that promotes the growth of pseudomonas. Whether this is due to the abnormally viscid mucus or the local calcium or chloride concentrations is uncertain. Colonization, which may not actually mean infection, with pseudomonas (mucoid colony type) leads to a state of chronic airway inflammation. This has been labeled frustrated phagocytosis. The inflammatory process directed against the pathologic organisms is incapable of eradicating the organisms and causes nonspecific damage to the airways that are "innocent" bystanders. Over time, this results in irreversible airway damage. This hyperimmune process is now known to be a major factor in the progressive lung disease that characterizes CF. Indeed, early studies showed that patients with hypogammaglobulinemia had less lung disease, fewer hospitalizations, and better oxygenation than those with normal or elevated levels of IgG (15). Indeed, those cystic fibrosis patients with the highest IgG levels had the worst prognosis and the shortest life expectancy (16). A study aimed at decreasing this hyperimmune process with prednisone therapy showed less progression of lung disease to controls (17). Unfortunately, the complications of steroid therapy were unacceptable. These include growth failure, development of cataracts and glucose intolerance. Further anti-inflammatory studies are underway.

The pulmonary disease is progressive, essentially unremitting and fatal. Therapy aimed at slowing this process includes mechanical mobilization of the thick secretions by chest physical therapy and postural drainage. This can be done by hand, mechanical percussors or by a vest percussion device. The use of nebulized rhDNase (Pulmozyme) (18) has been effective in decreasing the viscosity of CF mucus by aiding in the removal of the excessive DNA from the inflammatory cells destroyed in the airways. All of this is aimed at mobilizing secretions and encouraging expectoration.

Sputum cultures are used to define the organisms present. It is important to remember, however, that Staphylococcus aureus is frequently present in concentrations 100 to 1000 times less than that of the pseudomonas (19), such that Staph aureus is frequently undetected in routine (qualitative) sputum cultures. Quantitative culture, which would detect both organisms, remains a research tool unavailable to most clinicians. This could explain why CF patients with pseudomonas positive sputum cultures, improve on anti-staphylococcal antibiotics even after determining pseudomonas resistance to these antibiotics (20). In spite of this, antibiotic therapy aimed at specific organisms is a mainstay of therapy. Oral antibiotics are used when possible but hospitalization and intravenous antibiotics are frequently required. The timing of such intensive therapy in this chronic disease is best governed by symptoms as well as by objective pulmonary function data. Bacterial sensitivities are used to help select the best antibacterial agents. Usually, two antibiotics are used, an aminoglycoside and a anti-pseudomonal penicillin. Trials of single agents such as anti-pseudomonas cephalosporins (e.g. ceftazidime) continue. The aim is minimization of the yearly decrement in pulmonary function tests associated with the pulmonary deterioration. Nebulized therapy has offered an additional route for delivery of antibiotics (21). Twice daily aerosolized tobramycin (Tobi) has been used in a 28 day on, 28 day off pattern.

In spite of the large number of organisms present in the airways and sputum, CF patients rarely become septic and blood cultures are not helpful. It is an airway colonization process and not a pneumonic one.

One specific organism is known to be particularly worrisome. The acquisition Burkholderia cepacia is associated with rapid deterioration in pulmonary status and earlier death (22).

Other pulmonary complications include allergic bronchopulmonary aspergillosis (ABPA) (23) (another disease with airway colonization rather than tissue invasion), which requires corticosteroid treatment. Antifungal agents are not needed. Sinusitis is universally present in CF patients (24). Bronchospasm symptoms are treated with the usual medications outlined under asthma therapy. Pneumothoraces occur later in the disease and usually require chest tube drainage. Sclerosing agents, although effective in terminating persistent pneumothoraces (25), are relatively contraindicated since it may preclude lung transplantation (26). Hemoptysis is treated expectantly. Bronchial artery embolization has proven to be effective but has significant risks (27). Cor pulmonale is treated with oxygen therapy, diuretics and digoxin. Its presence is a sign of severe pulmonary disease and a poor prognosis sign (28).

Questions

1. The percentage of CF patients with pancreatic exocrine dysfunction (decreased lipase, amylase, etc.) is:
    a. 10%
    b. 25%
    c. 50%
    d. 85%

2. The carrier rate for the CF gene in the white population is:
    a. 1 in 10
    b. 1 in 15
    c. 1 in 25
    d. 1 in 50

3. The frequency of cystic fibrosis is:
    a. whites>blacks>latinos>asians
    b. whites>latinos>blacks>asians
    c. whites>asians>latinos>blacks
    d. latinos>whites>blacks>asians

4. An abnormal sweat test is:
    a. diagnostic of cystic fibrosis
    b. supportive of the diagnosis of cystic fibrosis
    c. has been replaced by genetic testing
    d. an abnormal sodium value

5. The most common CF gene is:
    a. R1066C
    b. Delta F508
    c. Not detected by genetic screening
    d. Present in less than 40% of patients

6. The percentage of CF patients with sinus opacification and/or infection is:
    a. 10%
    b. 25%
    c. 50%
    d. 75%
    e. 95%

7. What percentage of CF male patients have azoospermia
    a. 10%
    b. 25%
    c. 50%
    d. 75%
    e. 95%

8. The CFTR gene is located on chromosome:
    a. 5
    b. 7
    c. 9
    d. 11
    e. 13

9. The life expectancy of newly diagnosed patients with cystic fibrosis is:
    a. 5 years
    b. 10 years
    c. 15 years
    d. 20 years
    e. 30 years

10. Organisms characteristically isolated from the sputum of patients with cystic fibrosis includes all the following except:
    a. Staphylococcus aureus
    b. Streptococcus pneumoniae
    c. Klebsiella pneumoniae
    d. Pseudomonas aeruginosa
    e. Burkholderia cepacia

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Answers to questions
1.d, 2.c, 3.b, 4.b, 5.b, 6.e, 7.e, 8.b, 9.e, 10.b

Chapter VIII.4. Chronic Lung Disease of Infancy (Bronchopulmonary Dysplasia)

Mary Elaine Patrinos, MD

This 3 month old, former 26 week gestation male, presents to his pediatrician's office with a 2 day history of cough and fever. He was stable until 3 days ago when he had an episode of emesis followed by choking. His parents witnessed the episode, patted him on the back, and increased his oxygen flow rate from 1/4 to 1/2 liter/min due to cyanosis during and after the event. His temperature peaked at 39.6 degrees C (103.4 F) today. There has been no diarrhea or rhinorrhea. Oxygen saturation readings (SpO2) at home have been in the mid 90s. His diet consists of BPD formula, thickened with rice cereal. He has a decreased appetite. He continues to have 1-2 episodes of emesis per day.

PMH is remarkable for delivery at 26 weeks gestation. His neonatal course was characterized by respiratory distress syndrome (RDS) treated with surfactant, a patent ductus arteriosus (PDA) requiring ligation at 5 days of age, coagulase negative staphylococcus bacteremia, and retinopathy of prematurity (ROP). He required mechanical ventilation for almost 5 weeks and was successfully extubated after a brief course of systemic corticosteroids. He was also diagnosed with gastroesophageal reflux (GER). He was discharged from the hospital 3 weeks ago at 36 weeks postconceptional age (PCA). His medications include: Albuterol aerosols 1.25 mg TID, furosemide 3 mg PO QD.

Exam: VS T 39.2, P 175, RR 73, BP 96/58, SpO2 94% on 1/2 liter/min O2 by nasal cannula. He is a pink, slightly pale infant in moderate respiratory distress with an intermittent cough. The remainder of his exam is remarkable for moderate subcostal, intercostal, and substernal retractions. Breath sounds demonstrate fair aeration throughout, but they are decreased in the right upper lung field. Diffuse, soft wheezing is heard bilaterally.

A chest x-ray shows bilateral interstitial infiltrates, flattened diaphragms, and consolidation of the right upper lobe.

Chronic lung disease (CLD) is a disorder that originates in the neonatal intensive care unit, but regularly presents in the outpatient arena. Therefore, knowledge of the clinical presentation, pathophysiology, management, and outcome of bronchopulmonary dysplasia (BPD) is equally essential to the intensivist as it is to the primary care physician. The case above underscores many of the common features of the infant with chronic lung disease or bronchopulmonary dysplasia. As discussed in detail below, BPD is a chronic illness that is seen primarily in preterm infants. Additional risk factors noted in this patient are biochemical immaturity (surfactant deficiency), patent ductus arteriosus, mechanical ventilation, and oxygen therapy (Table 1) (1). BPD is a serious and potentially life threatening disorder. Originally described in 1967 by Northway, a radiologist, radiographic findings remain a major feature of the diagnosis and staging of the disease process. The definition of chronic lung disease has changed over the years. The older definition describes infants who remain oxygen dependent at 28 days of age or more (typically following a course of mechanical ventilation) and with abnormal radiographic findings. The more recent definition uses oxygen dependency at 36 weeks postconceptional age (PCA) as opposed to 28 days postnatal age (age since birth) to identify infants with BPD. This change in definition reflects a change in the patient population that has occurred over the last 20 years with an increase in the survival of extremely low birth weight infants (ELBW, <1000 g). The need for respiratory support is common in ELBW infants at 28 days of age, often due to respiratory insufficiency/immature respiratory mechanics and not lung injury (BPD) per se.

Table 1. Major Risk Factors Associated with BPD
Prematurity (anatomical and biochemical lung immaturity; antioxidant insufficiency)
Genetic predisposition
Fluid overload
Patent ductus arteriosus
Lung infection/inflammation
Air leak
Mechanical ventilation (barotrauma, volutrauma)
Oxygen
Malnutrition

The incidence of BPD increases with decreasing birth weight and gestational age such that approximately 15% of infants <1500 grams (g) and 50% of infants <1000 g are diagnosed with the disorder (1). The pathophysiology is based on the developing lung's vulnerability to various forms of injury. With the understanding that it is not "normal" for a 26 week gestation fetus to be outside of a fluid filled intrauterine environment, it is easy to appreciate how endotracheal intubation and mechanical ventilation can "do harm". This is, indeed, the neonatologist's major dilemma; providing support to an infant with immature respiratory physiology while minimizing iatrogenic injury. All aspects of patient care, nutrition, fluid administration, respiratory, infectious disease, etc., must be meticulously managed to curb the incidence and severity of chronic lung disease. Early in the disease process there is injury, inflammation, and capillary leak. Ongoing inflammation leads to fibroblast proliferation and scarring. Barotrauma or volutrauma causes airway epithelial and alveolar necrosis. If continued unchecked, the final outcome is a chronic pulmonary condition with features that include increased airway resistance and reactivity, mucous production, cystic emphysema, scarring, and atelectasis.

The clinical manifestations of chronic lung disease also evolve over time. In the early stages, tachypnea, retractions, cyanosis, and occasional grunting are seen. Later, reactive airway disease associated with wheezing and hypercarbia develops. Coexisting conditions such as feeding difficulties, poor growth, and gastroesophageal reflux (GER) may further complicate the clinical picture making these infants uniquely challenging and often frustrating to manage.

Prevention strategies are by far the most effective and satisfying in decreasing the incidence and reducing the severity of chronic lung disease. It is reasonable, based on the pathophysiology of BPD, that one approach might be to reduce an infant's exposure to mechanical ventilation and oxygen. Nasal continuous positive airway pressure (NCPAP) has been increasingly used to provide non-invasive respiratory support in the preterm infant. In addition, non-invasive means of monitoring oxygenation through the use of pulse oximetry allows for titration and reduction of supplemental oxygen to meet the infant's needs. Permissive hypercapnia, accepting higher levels of CO2, is also employed to reduce (wean or discontinue) ventilator support. Other approaches to prevention are listed in Table 2 (2), the most recent of which has been vitamin A supplementation. Vitamin A, necessary for epithelial integrity and healing, is often

deficient in preterm infants, (as are other cofactors, antioxidants, minerals, and trace elements). Recent studies have shown that vitamin A supplementation is beneficial in ameliorating the development and progression of chronic lung disease (3).

Table 2. Prevention Strategies for BPD
Antenatal corticosteroids
Surfactant
Postnatal steroids
Vitamin A
Permissive hypercapnia
Alternative ventilation strategies (synchronized, high frequency)
Fluid restriction
Balanced nutritional support

Various therapies have been developed to reduce symptom severity in the infant with BPD (Table 3). It is, indeed, the infant's good fortune that time is on his/her side! Because lung growth and development continues throughout infancy and early childhood, this is a disease process that the patient literally (completely or partially) outgrows. The goals of effective supportive therapy are to achieve adequate nutrition and growth while limiting episodes of disease exacerbation. It is, therefore, easy to understand why nutritional support serves as the mainstay of treatment. Caloric requirements for these infants sometimes exceed 140-150 kcals/kg/day. Increased metabolic demands coupled with feeding problems and GER, make this an especially challenging aspect of care. Parents share in the frustration of providing these infants with enough calories to grow and often suffer feelings of guilt in the process. Special formulas have been developed to increase caloric density (and intake), provide a proper balance of carbohydrate, protein, and fat, and limit free water. Preterm infant formulas (already 24 kcals/oz) are commonly used as the "base" which is further supplemented with protein, polycose (carbohydrate) and medium chain triglyceride (MCT) oil or vegetable oil to provide 30 kcals/oz. Indwelling nasogastric feeding tubes, and in some cases, gastrostomy tubes, are placed to provide enteral calories in infants with varying degrees of feeding difficulties. Close monitoring of an infant's growth is critical and, like all children, growth charts should be meticulously kept.

Table 3. BPD Treatment Strategies
Nutrition
Diuretics
Corticosteroids
Bronchodilators
Sodium cromolyn
Immunization (specifically, against RSV, respiratory syncytial virus)
Respiratory support (oxygen, CPAP, mechanical ventilation)

Diuretic therapy is common in the treatment of chronic lung disease of infancy. The rationale for diuretic use early in the disease process is to treat the pulmonary edema that accompanies inflammation and capillary leak. Later in the course, the lungs of BPD patients remain hydrophilic due to impaired lymphatic drainage from distorted architecture and decreased plasma oncotic pressure related to malnutrition and/or fluid overload (1). Cor pulmonale (right ventricular hypertrophy secondary to pulmonary hypertension), an end stage complication of severe BPD, also responds to diuretic therapy. Furosemide is the first line and most popular diuretic due to its additional benefits of venodilation and diminished airway reactivity. However, because of the multiple untoward side effects of furosemide, chlorothiazide (with or without spironolactone) is frequently used in "maintenance" therapy. Careful monitoring of electrolytes is essential with diuretic use. Bronchodilators are widely used to treat the reactive airway component of BPD. Inhaled agents include albuterol and ipratropium bromide. Rarely, in the most severe cases, theophylline may be employed as an adjunct to inhaled agents. Wheezing and CO2 retention are two of the major clinical manifestations of reactive airway disease. It is often beneficial to auscultate the chest before and several minutes following an inhalation treatment to determine its clinical efficacy. Confirming therapeutic benefit in the individual patient is important for determining ongoing management. Airway disease in these infants may sometimes be unresponsive to bronchodilator therapy.

The most controversial, but most effective short term treatment for CLD is dexamethasone. Clinical trials of dexamethasone treatment began in the early to mid 80s (4,5). The anti-inflammatory and pro-surfactant properties of corticosteroids made them a logical focus of study. These and subsequent studies have repeatedly demonstrated the positive short term benefits of corticosteroids as manifested by dramatic weaning of ventilator and oxygen support. As with many clinical trials, dosing amount, frequency, and treatment duration varied widely among studies. Adverse side effects, including hyperglycemia and hypertension, have also been documented. Subsequent trials of early dexamethasone use (within the 1st week of life) have shown greater risk than benefit (6,7). Therefore, if dexamethasone therapy is being considered, its use should be reserved for those patients with established chronic lung disease or prolonged ventilator dependency, typically older than 1 week of age (8,9). Of great concern is evidence suggesting that dexamethasone treatment is associated with an increase in developmental disability and cerebral palsy. It is the knowledge of the many serious side effects associated with systemic dexamethasone that has prompted clinicians and investigators to consider the use of hydrocortisone and inhaled corticosteroids in the prevention and treatment of chronic lung disease. Inhaled corticosteroids have been used in the treatment of adult and childhood asthma for many years. Limited studies in neonates have demonstrated no significant benefit beyond a reduction in the need for systemic steroid therapy (10). Logistical issues surrounding dosing and drug delivery in infants has further complicated this matter. Inhaled steroids are safer, but not without serious systemic side effects, especially at higher doses. Further information is needed before inhaled steroids become incorporated into the routine treatment of CLD.

The prognosis for BPD is largely dependent on its severity and the coexistence of other morbidities of prematurity (intraventricular hemorrhage/periventricular leukomalacia, short bowel syndrome, GER, and failure to thrive). As mentioned above, most infants outgrow their disease at varying rates. Despite the lack of clinical symptomatology in older children and adolescents, abnormalities often persist on pulmonary function testing. Less than 1% of ventilated preterm infants remain ventilator dependent for months or years. Aggressive measures to prevent and treat acute (respiratory) infections (hand washing, immunization, prompt use of antibiotics) must be instituted for an optimal outcome. Outside of the concerns regarding dexamethasone, it has long been recognized that infants with CLD are at high risk for neurodevelopmental delay and cerebral palsy which may occur in up to 28% of the time (1).

Infants with BPD are at risk for serious infections when they encounter respiratory viruses. A good example is respiratory syncytial virus (RSV), which typically presents as an upper respiratory infection in older children and adults and bronchiolitis in healthy infants. However, in infants with BPD, RSV pneumonia often occurs, which may result in apnea and respiratory failure. Prophylaxis against RSV has been available for the last 5 years to reduce the severity of infection. Passive immunization is available in two forms, a monoclonal antibody (palivizumab) and RSV immune globulin (RSV-IGIV). Palivizumab is administered monthly to high risk infants as an IM injection during the peak of the RSV season (November thru March) (11).

In summary, BPD or chronic lung disease of infancy is a disorder with a multi-factorial etiology. The smallest preterm infants are at highest risk due to the anatomical and biochemical immaturity of their respiratory, antioxidant, and immune systems. Prevention is the key to dealing with this disorder, however, once BPD develops, nutritional, respiratory, and developmental supportive therapies are critical to the successful management of these patients. Research is ongoing to further characterize the pathogenesis and explore safer and more effective options for prevention and treatment.

Questions

1. True/False: BPD is a common condition affecting most preterm infants requiring mechanical ventilation.

2. All of the following factors are included in the pathogenesis of chronic lung disease except:
   a. infection
   b. antenatal corticosteroids
   c. oxygen toxicity
   d. patent ductus arteriosus

3. Chronic lung disease is defined as:
   a. ventilator dependency at 2 weeks of age
   b. oxygen dependency at 36 weeks postconceptional age
   c. oxygen dependency at 28 days postconceptional age
   d. oxygen dependency at 28 days postnatal age
   e. b and d

4. An effective prevention measure for BPD is:
   a. surfactant therapy
   b. vitamin A supplementation
   c. fluid management
   d. management of patent ductus arteriosus
   e. all of the above

5. For adequate growth, infants with chronic lung disease frequently require a caloric intake of:
   a. 80 kcals/kg/day
   b. 100 kcals/kg/day
   c. 120 kcals/kg/day
   d. 140 kcals/kg/day

6. True/False: Inhaled corticosteroids are as effective as systemic steroids in the treatment of BPD, but with reduced side effects.

Related x-rays

Severe BPD case: Yamamoto LG. Severe Chronic Lung Disease and Respiratory Distress. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1995, volume 3, case 2. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v3c02.html

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Answers to questions
1. False, 2. b, 3. e, 4. e, 5. d, 6. False

Chapter VIII.5. Bronchiectasis in Children
Charles W. Callahan, DO

This is a 2-1/2 year old Polynesian male with a history of recurrent pneumonia who is now being hospitalized for symptoms of cough, wheezing and hypoxemia.

His past history is significant for dysmorphic features at birth which led to a diagnosis of a 5p chromosomal deletion consistent with Cri du Chat syndrome. He had difficulty in the neonatal period due to recurrent choking episodes and a presumed poorly coordinated swallow. He was initially discharged on oral feedings; however, he developed several episodes of pneumonia and reactive airway disease, for which he received treatment. At 15 months of age, an ambulatory evaluation for chronic aspiration was conducted because of recurrent wheezing. A modified barium swallow revealed mild dysfunction of the oral phase of swallowing with a delay in bolus transfer, especially evident with liquids. There was no pooling or aspiration noted. A nuclear scintiscan revealed eight episodes of gastroesophageal reflux (GER) to the hypopharynx, without evidence of aspiration. He was treated with cisapride and ranitidine. Despite this, he was hospitalized 4 more times for lower respiratory exacerbations. He is now being hospitalized for evaluation and treatment of an exacerbation consisting of coughing, wheezing and hypoxemia. A pediatric pulmonologist is consulted.

His family members are all healthy except for a family history of asthma.

Exam: T 37, P 97, R 40, BP 99/64, oxygen saturation 91% in room air. Weight 11 kg (<5%ile). He is alert in no acute distress but he is episodically tachypneic. Auscultation of his chest reveals heterophonous (small airway) and homophonous (large airway) wheezing with diffuse fine crackles. Examination of his upper and lower extremities reveals moderate digital clubbing. A chest radiograph shows bibasilar reticulonodular opacities that have been essentially unchanged for almost one year, with new right middle lobe disease.

A thin section, high-resolution computed tomography (HRCT) scan of his chest shows bibasilar thickened and dilated bronchi consistent with cylindrical bronchiectasis. CBC, electrolytes, UA, sweat chloride, ANA, immunoglobulins, alpha-one antitrypsin and fungal serology are all negative. Bronchoscopy with bronchoalveolar lavage reveals erythematous, friable airways with no obvious airway anomalies. Lavage revealed a cell count of 750 per microliter, of which 105 were red blood cells and the remainder white blood cells (70% neutrophils and 30% macrophages). Gram stain shows no organisms. Cultures are not definitive. Staining of the lavage fluid with oil red-O reveals numerous lipid-laden macrophages (a marker of chronic aspiration). A hemosiderin stain (evidence of chronic bleeding) is negative.

A nuclear scintiscan repeated on cisapride and ranitidine shows mid-esophageal GER. He is placed on cefuroxime for presumed bacterial bronchitis despite inconclusive cultures. More importantly, he is also started on nasogastric feeds and is not allowed to take anything by mouth. Within days, his pulmonary signs and symptoms improve markedly. He later undergoes a Nissen fundoplication with gastrostomy tube placement. After six months of gastrostomy feedings while remaining NPO, he is clinically improved, having gained weight and tolerated minor upper respiratory infections without hypoxemia. Seven months post-procedure, he has a follow up HRCT scan of his chest that shows near resolution of his bronchiectasis. His digital clubbing eventually resolves and a chest radiograph shows no suggestion of bronchiectasis.

Bronchiectasis is a chronic lung disease whose pathophysiology is poorly understood. It has traditionally been considered "permanent and irreversible" (1). Traction of airways from collapsed surrounding structures, bulging of the airways from retained secretions, weakening of the bronchial wall by infection or inflammation, or combinations of these factors are all suggested mechanisms (2). Single or repeated acute infections, chronic obstruction from congenital anomalies, tumors, cystic fibrosis, chronic asthma or immunodeficiencies may also predispose a patient to developing the disease (3). In addition, repeated airway injury from chronic aspiration, with or without gastroesophageal reflux (GER), has been implicated as another etiologic possibility (4,5).

Bronchiectasis has been termed an "orphan disease" which may not always be considered in the evaluation of children with obstructive pulmonary disease because it has become relatively uncommon in the antibiotic era (1,5). Fifty years ago, Field studied 160 children with bronchiectasis for almost 2 decades (6,7,8,9). In that period, she documented a fall in the annual hospitalization rate for bronchiectasis in five British hospitals (1952-1960) of approximately 48/10,000 to 10/10,000 (9). At our institution among children of American Military members, there have been 14 pediatric cases in the past 19 years including the present case, yielding an approximate rate of 0.2/10,000 (unpublished data).

The term "bronchiectasis" has traditionally implied permanent, irreversible alteration in the anatomy of the airways (1,10). It has been classified as cylindrical, varicose or saccular (1,10). The diagnosis should be considered in children with daily, productive cough of longer than 6 weeks duration, hemoptysis, children with persistent radiographic infiltrates, digital clubbing or isolated, persistent crackles on auscultation. (6,10). Traditionally, the diagnosis was made by bronchography (chest radiograph taken with inhaled contrast), as the plain chest radiograph is relatively insensitive for the detection of bronchiectasis (10). Most commonly today, the diagnosis is made by thin-section high resolution CT scan. The diagnosis is based upon the presence of an internal bronchial diameter greater than the adjacent pulmonary artery, lack of tapering of the bronchial lumina, and visualization of the bronchi within 1 cm of the pleura, although the use of the first of these criteria has been debated (11,12).

The combination of small airway obstruction coupled with chronic inflammation of the bronchial wall is most likely the mechanism in the development of bronchiectasis. The inflammation usually results from acute or chronic bacterial infection or "colonization" of the airways (7,10,13). The majority of cases of bronchiectasis follow severe pneumonia or other lower respiratory infection (10). In a series by Field fifty years ago, 24% of cases followed pneumonia, and 33% followed some combination of pertussis and/or measles infections (6).

Chronic aspiration, either from cricopharyngeal dyscoordination or gastroesophageal reflux, is a recognized condition that can lead to bronchiectasis in adults and children (5,10). It has probably emerged as a more common cause as antibiotics and vaccinations have diminished the other infectious etiologies. In addition, bronchiectasis has been shown to be more common in patients of Polynesian descent (13,14). A ciliary defect is thought to be the etiology but has not been consistently demonstrated (15). Bronchiectasis has also been reported with increased frequency in Native Alaskan children, although some theorize that the common thread is a low socioeconomic level (16,17).

Bronchiectasis, particularly the mildest of the pathologic forms, cylindrical bronchiectasis, may be reversible. When associated with pneumonia, it may resolve with treatment of the acute process (18). Resolution of post-obstructive bronchiectasis has even been reported after removal of a chronic foreign body (19). Some refer to this as "pseudobronchiectasis" (10).

Clubbing is reported in 37-51% of patients with bronchiectasis. In Field's series of 160 patients with bronchiectasis, clubbing was present in 78 cases (44%) (6). In many cases, the clubbing cleared after the affected section of the lung was removed surgically. In cases treated medically, occasionally the clubbing improved and in some cases it disappeared despite persistent bronchographic evidence of bronchiectasis (6). Of interest, Field concluded, "clubbing when present, usually signified irreversible bronchiectasis, providing there was no congenital cardiac lesion" (6).

In the same patient series, Field also described the condition of "reversible bronchiectasis," a temporary dilation of airways in areas of the lung that had been collapsed due to infection or atelectasis (7). She suggested that duration of cough and pulmonary symptoms was commonly of three months duration or less in children with reversible bronchiectasis and pulmonary collapse which reexpanded. In the same series, the majority of children with a history of symptoms for two years or more generally developed severe bronchiectasis (7).

The evaluation of a child with bronchiectasis should include an evaluation for any identifiable cause of the condition. Testing for cystic fibrosis with a sweat chloride test as well as genotype determination should be performed in select cases. Children in their first two decades do not usually develop lung disease from alpha-one protease inhibitor deficiency, but a level should be obtained. Other congenital conditions such as Mounier-Kuhn (congenital absence of airway muscle) and Williams-Campbell (congenital absence of airway cartilage) can usually be suspected from the radiograph and CT scan. Marfan's, Ehlers-Danlos, and the Yellow-Nail syndrome all have other phenotypic findings (5).

Post infectious causes of bronchiectasis are harder to prove. The child should have a PPD with anergy panel to assess for TB. Evaluation for allergic aspergillus or allergic fungal disease should be considered. Serum levels for pertussis, measles and adenovirus are probably not helpful in a child with bronchiectasis because of immunization and the possibility of previous, unrelated disease (5).

Basic aspects of the immune system should be evaluated including serum immunoglobulins and serum IgE. There are cases of bronchiectasis preceding other symptoms of rheumatic disease, sometimes by decades, so an anti-nuclear antibody and rheumatoid factor should be obtained. Finally, a thorough evaluation for gastroesophageal reflux should be undertaken including extended intraesophageal pH probe monitoring (5).

Children with bronchiectasis should be treated with antibiotics during symptom exacerbations based upon sputum culture results. Exacerbations should also be treated with increased frequency of the daily regimen of chest physiotherapy and postural drainage, usually conducted twice a day. Intense aerobic exercise is another, excellent means of pulmonary toilet. Bronchodilators are indicated where there is evidence of bronchial hyper-reactivity (8,9,10,13). There may also be a role for inhaled corticosteroids to modulate the host response and curb inflammatory damage to the lung (13). Therapy for an identified cause of bronchiectasis should be undertaken, including aggressive medical and perhaps even surgical therapy for gastroesophageal reflux.

When damage is severe and well localized, pulmonary segmental resection may be beneficial (8,9,10). However, Field demonstrated a gradual symptomatic improvement of children who did not have surgical therapy for bronchiectasis, even before the proliferation and availability of broad spectrum antimicrobials (9). Lewiston recommended that surgery be delayed unless symptomatically necessary, until the patient is 6-12 years, because of the possibility of clinical improvement (10).

Bronchiectasis has become an uncommon disease in the developed world, but it may often be unrecognized. It should be suspected in children with chronic respiratory symptoms, since it is often amenable to long-term medical management. Surgical therapy should be reserved for situations of recurrent pulmonary sepsis unresponsive to aggressive medical management.

Questions

1. True/False: Causes of bronchiectasis in childhood include cystic fibrosis, asthma and immunodeficiency.
2. True/False: Bronchiectasis has been traditionally classified as round, cylindrical or cavitating.
3. True/False: Most commonly today, bronchography is required for the diagnosis.
4. True/False: Chronic aspiration is a recognized cause of bronchiectasis in children.
5. True/False: Children of Polynesian descent are at no increased risk of bronchiectasis.
6. True/False: Therapy for bronchiectasis in children includes early surgical resection.

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Answers to questions
1. true
2. false
3. false
4. true
5. false
6. false

Chapter VIII.6. Foreign Body Aspiration
Edward W. Fong, MD

A mother brings her 14 month old son into the urgent care clinic with complaints of choking and gagging after eating potato chips 15-20 minutes ago at his grandmother's house. His mother is unsure if he had eaten anything else with the potato chips and does not think the child turned blue during the choking and gagging episode. He returned to his normal activity shortly after the episode occurred, but since then, he has had a few intermittent coughing spells. The patient has two older siblings who are still at the grandmother's house.

Exam: VS T 37.2, P 103, R 28, BP 98/55, O2 saturation 96% in RA, height/weight/head circumference are all 25-50%ile. He is walking around the exam room in no acute distress. He has a normal physical exam except for an occasional low-pitched, monophonic expiratory wheeze heard best over the sternal notch.

A CXR is obtained which appears normal. Since end exhalation films were unable to be obtained, decubitus films were performed. The right lateral decubitus film (right side down) shows air trapping on the right as evidenced by failure of the mediastinum to shift toward the dependent side. A pediatric surgery consult is obtained and they take the child to the OR for rigid bronchoscopy. They find a whole sunflower seed in the right main stem bronchus and remove it. The child is then hospitalized overnight for observation and chest physiotherapy (CPT) that is ordered for atelectasis seen on a post-op film. Upon arrival of the patient's grandmother to the hospital, further history elicited from her is significant for the older siblings eating sunflower seeds. The patient is discharged the next morning with follow up scheduled with his pediatrician in the next few days.

Foreign body aspiration is a very serious, often life-threatening, condition. According to the 1998 National Safety Council statistics for the United States, 3% of all unintentional deaths among children (<15 years old) were secondary to the inhalation/ingestion of food or objects (IOFO) (1). In fact, 5% of all IOFO deaths occur in this age group. IOFO is the 5th leading cause of death in the United States and Hawaii for all age groups (1). Of children younger than 15 years, toddlers seem to be the most vulnerable for foreign body aspiration (77% of deaths) (1). Some reasons for this are related to their developmental age such as: 1) exploration of their environment by putting objects into their mouths; 2) learning to walk and run; 3) inadequate dentition; 4) immature swallowing coordination; and 5) supervision by an older sibling. Baharloo, et al, found that 91% of foreign bodies aspirated by children (<8 years old) were organic in nature with peanuts accounting for 54% of that number (2). Meat (especially hot dogs) and other types of nuts are also frequently found on bronchoscopy. They also found that children, unlike adults, did not have a significant difference between the foreign body being found in the right or left bronchial tree (2). This may be explained by the fact that children have symmetric bronchial angles until about 15 years of age. At that time, the aortic knob has developed fully, causing the left mainstem bronchus to be displaced, which creates a more obtuse angle at the carina favoring the right mainstem for a foreign body (3).

There are three distinct clinical phases that occur after a foreign body is aspirated (4). The first phase occurs immediately following the incident. The patient will usually experience choking, gagging, coughing, wheezing, and/or stridor. There may also be an associated temporary cyanotic episode, usually perioral. The occurrence of death is very high during this first phase of aspiration. The second phase is the asymptomatic period that can last from minutes to months following the incident. The duration of this period depends on the location of the foreign body, the degree of airway obstruction, and the type of material aspirated. The ease with which the foreign body can change its location is also a factor in the duration of this period. The third clinical phase is the renewed symptomatic period. Airway inflammation or infection from the foreign body will cause symptoms of cough, wheezing, fever, sputum production, and occasionally, hemoptysis.

There are several conditions that could mimic an aspirated foreign body. Some of these illnesses are: asthma, croup, pneumonia, bronchitis, tracheomalacia, bronchomalacia, vocal cord dysfunction, or psychogenic cough (4).

The diagnosis and treatment of an aspirated foreign body depends on which clinical phase the patient has on presentation. History, as always, is the best determinant of how suspicious one should be of a potential aspiration. However, this is often complicated by the fact that the event may be unwitnessed, witnessed by a person not present for history taking, or witnessed by an older sibling who may have had a role in the aspiration and chooses not to say anything. On physical exam, the classic findings consist of cough, unilateral decreased breath sounds, and unilateral monophonic wheezing. Although 75% of patients have one or more of these findings, only 40% have all three (5). If stridor (inspiratory and/or expiratory), aphonia, or hoarseness is present, the foreign body is most likely in the larynx or cervical trachea. The usefulness of diagnostic imaging is variable. Since most foreign bodies are not radiopaque, one must rely on indirect findings suggestive of the presence of a foreign body such as: mediastinal shift, atelectasis, and hyperinflation. It has been reported that imaging studies have a sensitivity of 73% and a specificity of 45%, however, up to 20% of patients will have both negative history and radiographic evaluation (6).

For patients who present early, radiographic studies must look for evidence of air trapping. Some clinicians have been taught to look for asymmetry on an expiratory view. However, many foreign body aspirations involve both main stem bronchi or the foreign body is in the trachea. Thus, asymmetry is not seen in these instances. Identification of air trapping is the key. If the expiratory view looks the same as the inspiratory view, this implies bilateral air trapping. Asymmetry suggests unilateral air trapping. Expiratory views rely on timing, so these are sometimes deceiving (an "expiratory view" could have been really taken during inspiration). Decubitus views may be more reliable in this regard. In a lateral decubitus view, the mediastinum should shift downward toward the dependent side. Failure to see this implies air trapping on the dependent side. Thus, if a decubitus view looks the same as an upright inspiratory view, this suggests air trapping on the dependent side.

If the patient presents in the first clinical phase, the family and/or health care professional should be advised to follow the recommendations of the American Academy of Pediatrics and American Heart Association (7). Unless there is a complete airway obstruction, spontaneous coughing and respiration should be the only treatment encouraged. Blind finger sweeps should never be performed in infants or children since this may push the foreign body further downward into the airway. Infants with complete airway obstruction should have back blows and chest thrusts performed while children with complete airway obstruction should have abdominal thrusts performed in either the supine position or by the Heimlich maneuver. Once the patient is brought to the hospital, the patient will require rigid bronchoscopy for visualization of the airway and removal of the foreign body. Flexible bronchoscopy does not have a role in this situation because it is not the optimal tool for control of the foreign body or the safety of the patient during the removal procedure.

The other situation in which patients commonly seek medical attention is usually the third clinical phase. At this point in time, clinical suspicion based on the history, exam, and ancillary studies must be used to determine the appropriate course of action. Patients may present with signs and symptoms of pneumonia. In many such instances, a foreign body is not suspected and the foreign body remains untreated. Such patients return with "recurrent pneumonia" which is actually a pneumonia or atelectasis which has never resolved because the foreign body is still there.

If foreign body aspiration is suspected in this phase, the patient should undergo direct airway visualization by bronchoscopy (flexible or rigid). Even if the patient has expectorated a foreign body, direct visualization is recommended to ensure there are no additional foreign bodies present and to determine if there is any compromise of the airway from inflammation. Medical management (from expectant management to CPT with bronchodilator therapy) should not be done in this situation because the object could become dislodged causing a complete airway obstruction (4). However, once the foreign body is removed, CPT and bronchodilator therapy could help with complications such as atelectasis. If there is airway edema and/or inflammation present on direct visualization, a short course of oral corticosteroids may be useful. Unless there are signs or symptoms of an infection (tracheitis, pneumonia, etc.), antibiotics need not be used.

Complications arising from foreign body aspiration depend on the location and type of foreign body aspirated (organic vs. non-organic, sharp vs. dull), and the duration of time the foreign body remained in the airways. If the foreign body is successfully removed within 24 hours of the incident, the complication rate is very low. However, the longer the foreign body remains in the airways, the more likely inflammation and thus, complications will occur. Potential complications include: bronchial stenosis, bronchiectasis, lung abscess, tissue erosion/perforation, and pneumomediastinum or pneumothorax.

Questions

1. True/False: Foreign body aspiration is sufficiently uncommon that it need not be considered in a patient with a chronic cough.

2. Which radiographic imaging study would be the most helpful if a foreign body aspiration is suspected in a child (<3 y.o.)?
   a. PA
   b. Inhalation/Exhalation
   c. Lateral
   d. Decubitus

3. Describe the three clinical phases of foreign body aspiration.

4. What would be worse to aspirate: organic or non-organic material? Why?

5. True/False: Aspirated foreign bodies in children are more likely to be in the right main-stem bronchus than the left main-stem bronchus.

6. Why should a blind finger sweep never be done in a child with a foreign body aspiration?

7. What physical exam sign/symptom is most suggestive of foreign body aspiration?
   a. Fever
   b. Polyphonic wheezing
   c. Cough
   d. Stridor
   e. Monophonic wheezing

8. What physical exam sign/symptom is most worrisome in terms of degree of airway compromise?
   a. Fever
   b. Polyphonic wheezing
   c. Cough
   d. Stridor
   e. Monophonic wheezing

9. True/False: Nuts + Choking = Bronchoscopy

Related x-rays

Foreign body aspiration case: Boychuk RB. Foreign Body Aspiration in a Child. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1994, volume 1, case 8. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v1c08.html

Foreign body aspiration case: Feng AK. Recurrent Pneumonia. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1995, volume 2, case 7. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v2c07.html

Miscellaneous chest x-rays with foreign body aspiration case: Yamamoto LG. Test Your Skill In Reading Pediatric Chest Radiographs. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1995, volume 3, case 20. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v3c20.html

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Answers to questions

1. False.
2. d.
3. First phase: Acute symptomatic period that immediately follows the incident. May see choking, gagging, coughing, and/or cyanosis. High risk of death. Second phase: Quiescent asymptomatic period. May last minutes to months depending on location, type, and ease of movement of the foreign body. Third phase: Renewed symptomatic period. May see wheezing, chronic cough, fever, hemoptysis. High risk of complication.
4. Organic material is worse to aspirate because it will cause a more intense inflammatory response, thereby increasing the risk for complications. Additionally, most organic material is non-radiopaque making it more difficult to visualize.
5. False. Right and left foreign bodies occur at roughly the same frequency.
6. A blind finger sweep may reposition the foreign body causing a complete airway obstruction.
7. d
8. d
9. True. Whenever a choking episode occurs while a young child is eating nuts, the risk of foreign body aspiration is high. Bronchoscopy should be highly considered here (9).

Chapter VIII.7. Pulmonary Hemosiderosis
Scott J. Sheets, DO

This is an 8 month old male referred to Pediatric Pulmonary Clinic with a chief complaint of chronic cough. The cough has been present for 7 weeks. Initially, it was attributed to a viral illness, but the viral cultures and screen for RSV were negative. The cough improved but did not clear with bronchodilators and an aggressive short course of oral corticosteroids which were instituted for suspected asthma. The symptoms had worsened again after the bronchodilator and steroid trial was discontinued. There is a low-grade fever but no evidence of a new upper respiratory infection. The chest radiographs performed by the patient's primary care physician shows worsening diffuse patchy consolidations with hyperexpansion. Review of systems reveals a slowing of growth from the 4 month routine well child visit to present. There is no family history of any respiratory disease, chronic or serious medical conditions.

Exam: VS T 37.0, P 140, R 50, BP 100/60, pulse oximetry showed oxygen saturations of 86% in room air. His weight is at the 5th percentile. He is thin, slightly pale, tachypneic with slightly labored breathing. HEENT exam is normal. His chest has symmetrical expansion. There are mild subcostal retractions, but no intercostal or supraclavicular retractions are seen. His heart is tachycardic but regular without murmurs. His breath sounds are coarse on inspiration and expiration throughout. The expiratory phase is slightly prolonged. There is good air exchange. His abdomen is soft, non-distended with normal bowel sounds and no hepatosplenomegaly.

Oxygen is started by mask and he is admitted to the hospital. Bronchodilators and antibiotics are initiated and corticosteroids are resumed. His oxygen saturation only improves slightly with supplemental oxygen. The arterial blood gas shows pH 7.35, pCO2 34, pO2 55 on 2 liters/minute of supplemental oxygen. His CBC shows a mild elevation of the white blood count, a normal platelet count, and an anemia with hematocrit of 26, a mean corpuscular volume of 76, and red cell distribution width of 15. His eosinophil count is modestly elevated. Iron studies show depleted iron stores. His chest radiograph still shows interstitial infiltrates.

His improvement over the next three days is gradual, and his chest radiograph still shows an interstitial pattern. Bronchoscopy is performed. The bronchoalveolar lavage demonstrates a large number of hemosiderin-laden macrophages. Cultures and lipid-laden macrophages are negative.

After further review of his history, he had been constipated on formula for the first few months of life, so he was switched to regular cow's milk and juice at 3 months of age. The serum IgG precipitins to cow's milk protein are strongly positive. The diagnosis of Pulmonary Hemosiderosis by Heiner's syndrome is made. All cow's milk and milk products are withheld. His clinical condition rapidly improves. His subsequent chest radiograph clears with only persisting streaky consolidations. After one week of corticosteroids, they are discontinued. He is continued on iron supplementation and his anemia slowly resolves. Growth also normalizes over the next 3 months.

Any bleeding from or into the lung will lead to hemosiderin deposits in the lung macrophages. Pulmonary Hemosiderosis (PH) is a term that should be reserved for chronic persistent or recurrent bleeding. It is a complex topic, covering a spectrum of different conditions and disease states. The clinical presentation and course is highly variable. Bleeding can be focal or diffuse. It can occur in the airways, alveoli or parenchyma. It can be from pulmonary (lower pressure) or bronchial circulation (higher pressure). It can be mild or life threatening. While there is no universal agreement in classification, it is useful to categorize PH as either primary or secondary (1-3). The following table categorizes the etiologies of Pulmonary Hemosiderosis in children from the standpoint of whether the lung insult is primary or secondary:

1. Primary Pulmonary Hemosiderosis (PPH)
   A. Idiopathic (IPH).
   B. Associated with certain molds or fungi (Stachybotrys atra) (4).
   C. Associated with cow's milk allergy (Heiner's syndrome) (5).
   D. Associated with antibody to basement membrane of lung (Wegener's granulomatosis) and kidney (Goodpasture's syndrome).
   E. Trauma including foreign body aspiration.
   F. Bronchiectasis and other chronic lung infections.
2. Secondary Pulmonary Hemosiderosis
   A. Pulmonary vascular disease including cardiac disease, pulmonary hypertension and arteriovenous malformations.
   B. Generalized systemic inflammatory disease.
   C. Generalized bleeding disorders, including purpuric syndromes and coagulopathies associated with sepsis.
   D. Ingestion of drugs or chemicals such as Trimellitic anhydride or D-Penicillamine.

The pathophysiology of pulmonary hemorrhage varies by the etiology. Bleeding can come from inherited or acquired weakness, inflammation or congestion of pulmonary blood vessels; immune reactions or antigen-antibody complex deposition in the lung; invasive or chronic infections, or toxic reactions. Regardless of the, any blood cells in the alveoli, airways or parenchyma, are broken down and the hemoglobin is ingested by local macrophages. Once ingested, the hemoglobin is converted to hemosiderin by lysosomal degradation. It may also activate the local macrophages, followed by an inflammatory cascade, including the recruitment of cells and production of cytokines. These events can produce all types of lung disease, pulmonary consolidations, and lymphadenopathy.

Obstructive disease can be seen as the airways narrow with an increase in edema, mucus production and shedding of epithelial cells into the airway. Bronchospasm (the contraction of smooth muscle surrounding the airways) can be seen. Chronic accumulation of fibrin and collagen deposits can lead to pulmonary fibrosis with decreased pulmonary compliance. This can manifest as a restrictive lung disease pattern.

Pulmonary hemosiderosis is an uncommon finding, but the true incidence is unknown. Primary PH is more common in children. The peak incidence of IPH (idiopathic) is between 1-7 years of age at diagnosis, but approximately 15% are diagnosed after 16 years of age. Below the age of 10, the incidence is equally divided between the sexes. After age 10, the male to female ratio is 2:1 (7). There are rare instances of familial clusters reported. In adults, PH is more likely to be secondary in nature.

The classic triad of findings includes pulmonary infiltrates, iron deficiency anemia and hemoptysis (although hemoptysis is seen less commonly in children). Approximately 50% of young children present without pulmonary complaints. When present, complaints include fever, pallor, dyspnea, cough, exercise intolerance and growth failure. Common findings are, tachypnea, tachycardia, cyanosis, clubbing, fine or coarse crackles, wheezing, and hypoxemia. In children with a significant hemorrhage, it may be difficult to determine

whether the blood is coming from the upper airway, lower pulmonary system or GI tract. Many patients will have melena from swallowed pulmonary blood.

The radiographic appearance may vary depending on the degree of involvement and chronicity. Plain film chest radiographs may range from normal to demonstrating focal lymphadenopathy or consolidations, or extensive bilateral interstitial disease. Pulmonary function testing may demonstrate an obstructive, restrictive or mixed pattern.

It is common for patients with PH to have a delay in diagnosis. Infectious pneumonia, bronchitis, aspiration, asthma and cystic fibrosis are more commonly seen with many of the same complaints and findings. Having a high clinical suspicion is necessary to make the diagnosis. While a bronchoalveolar lavage finding of a large number of hemosiderin-laden macrophages is diagnostic, it is not the end of the evaluation. Subsequent studies are needed for evaluation of the etiology. IPH is a diagnosis of exclusion, and is only appropriate after a thorough investigation is completed.

Complete blood counts, iron studies and a measure of renal function will be helpful to evaluate the patient's current status. ANA, rheumatoid factor, erythrocyte sedimentation rate, complement levels, immunoglobulins, anti-basement membrane antibodies, and serum precipitins to cow's milk protein should also be included in the evaluation for etiology. A cardiac evaluation including physical exam, EKG and CXR evaluation should be included. A referral to cardiology, rheumatology or hematology should be considered. Some experts advocate a lung biopsy for all patients, to include immunofluorescence and electron microscopy studies. Others reserve this for selected cases.

Each patient should have supportive measures as appropriate to their presentation, including supplemental oxygen, blood transfusion, and antibiotics for cases of secondary infection or suspected infection. Respiratory support includes chest physiotherapy to aid in clearing excess secretions, bronchodilators, CPAP or mechanical ventilation. Patients with ongoing bleeding may benefit from positive end expiratory pressure (PEEP).

Treatment has to be viewed in light of the etiology. For those with PH from exposure and toxins from Stachybotrys, the main treatment is elimination of the offending agent. Diet restriction, especially for those found to have serum precipitins to milk products, is essential. For those with secondary PH, treating the primary etiology is critical.

Medical therapy is typically aimed at controlling the inflammatory response. Corticosteroids are the mainstay, but there is no study comparing the dosing strategy. The dose is usually started at 2-5 mg/kg/day of prednisone or equivalent. This dose is used for several weeks, or until the hemorrhage is well controlled. The dose is then tapered, and there are many different protocols. Other immunosuppressive agents have been used in an attempt to reduce the prolonged corticosteroid effects, including azathioprine, chloroquine and cyclophosphamide.

If patients are having significant ongoing hemorrhage, a nuclear medicine study with labeled RBCs can be done to help locate the site. For life-threatening bleeds or those patients that don't respond to medical therapy, bronchial artery embolization may be required. For extreme cases removal of an affected segment or lobe may be necessary.

Close monitoring should include growth, oxygen saturation monitoring, hemoglobin and iron studies, chest radiographs, pulmonary function testing (if old enough), and renal function studies throughout recovery. Reinstitution of aggressive corticosteroid or immunosuppressive therapy is typical for breakthrough exacerbations.

The prognosis is variable, related to the cause. For secondary PH, it must include the natural history of the primary disease. A delay in diagnosis will yield a worse prognosis. Early studies showed a very poor prognosis for IPH. The average was approximately 2 years from diagnosis to death. More recent reports suggest an improvement in this statistic with more aggressive management (8,9). Additionally, newer technology has provided the means for more extensive evaluation, facilitating specific diagnostic determination (i.e., fewer diagnosis of IPH). Many patients can have sustained or complete remission with newer therapies. Although scarring and fibrosis may be permanent, full compensation is possible, especially in younger patients.

Questions

1. Which of the following findings are not usually present in a patient presenting with pulmonary hemosiderosis?
    a. Fever
    b. Parenchymal consolidations
    c. Hypercarbia
    d. Hypoxemia
    e. Cough

2. Why is it important to classify hemosiderosis as primary or secondary?

3. What kind of lung disease can be seen in pulmonary hemosiderosis?
    a. Obstructive disease
    b. Restrictive disease
    c. Mixed obstructive and restrictive
    d. Any of the above

4. Which of the following is not part of the classic triad of symptoms seen in pulmonary hemosiderosis?
    a. Pulmonary hemorrhage
    b. Anemia
    c. Hemoptysis
    d. Pulmonary infiltrates
    e. None of the above

5. True/False: Lung biopsy is the diagnostic test of choice for idiopathic pulmonary hemosiderosis.

Related x-rays

Goodpasture's Disease case: Nakamura CT. Hemoptysis and Anemia in a 12-Year Old. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1995, volume 3, case 7. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v3c07.html

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Answers to questions

1. c. Hypercarbia is not usually seen because compensatory mechanisms usually overcome the problems of reduced gas exchange by increasing minute ventilation (either by increasing rate or depth of ventilation).

2. It is one scheme to help identify the etiology for a condition with numerous causes. Treatment is more likely to be successful after identifying and treating the primary cause.

3. d. Bronchospasm, edema, and mucus can narrow the airway causing obstructive disease similar to asthma. Chronic inflammation can increase interstitial fibrin and collagen deposits which then reduce compliance resulting in giving restrictive disease. Any combination of the two is possible.

4. a. The classic triad is iron deficiency anemia, pulmonary infiltrates and hemoptysis, although hemoptysis is seen less commonly in children. "Pulmonary hemorrhage" does result in hemosiderosis, but it is not part of the classic triad.

5. False. There is controversy over whether a lung biopsy should be undertaken for all patients with significant PH. It could be argued that all patients who have PH without a known etiology (suspected IPH) should have a lung biopsy. But since IPH is a diagnosis of exclusion, a lung biopsy doesn't preclude the other parts of the evaluation, including history, exam, radiology and laboratory studies. Pathology from lung biopsy is seldom diagnostic alone and can only be interpreted in light of the other information.

Chapter VIII.8. Pulmonary Vascular Anomalies
Jason H. Brown and Edward W. Fong, MD

This is a 5 year old female who presents to the clinic with shortness of breath, a cough with "lots of mucus" for the last two days, and fever as high as 39.0 degrees C two days ago to 37.0 degrees C this morning. Her parents are worried that she has been getting many chest colds with fevers for the last year and that she coughs and feels out of breath even when she isn't sick. Dextromethorphan cough syrups have not helped her symptoms. Exertion makes her cough worse. There are no other associated symptoms including muscle weakness, cyanosis, hemoptysis, chest pain or dizziness. Her past medical history shows no major illnesses or hospitalizations. Her growth and development have been good. Her family history is not contributory. Review of systems is non-contributory.

Exam: VS T 37.0, HR 85, RR 40, BP 110/68, oxygen saturation 97% in room air. Height and weight are at the 25th percentile. She is a pleasant, comfortable, alert, well-developed, well-nourished 5 year old who is non-toxic and in no acute distress. HEENT and neck exams are normal with no lymphadenopathy. Her cardiac exam is abnormal with the PMI 3 cm right of the midline of the sternum, a palpable sternal lift, a widely split S2, and a grade 2/6 systolic ejection murmur heard greatest over the pulmonic area. Some jugular venous distention is also present. Her respiratory exam shows moderate tachypnea with normal chest percussion and symmetrical chest movements. Some fine crackles are heard throughout the lung bases bilaterally. Her abdomen is soft and non-tender, but notable for hepatomegaly with the inferior liver margin extending 4 cm below the right costal margin. Her back is non-tender. Her extremities show normal muscle bulk, tone and strength, with normal DTRs and peripheral pulses.

A CXR shows dextrocardia, cardiomegaly, right lung hypoplasia, a dilated right main pulmonary artery, increased right pulmonary vascular markings, and right-sided pulmonary infiltrates versus atelectasis. A large vein in the right hemithorax raises the possibility of scimitar syndrome. An EKG shows right axis deviation (presumably due to dextrocardia), but is otherwise normal. An echocardiogram shows a dilated right atrium and right ventricle consistent with volume overload and 2 aberrant veins draining 70% of the pulmonary venous return into the vena cava instead of the left atrium. A large 1.5 cm artery off the aorta is present, feeding into the right lower lobe. No ASD (atrial septal defect) is found. CT scans confirm the findings of the echocardiogram. A cardiac catheterization is performed to determine the pressure in the left atrium, which is found to be elevated.

She is diagnosed with pneumonia and scimitar syndrome consisting of 2 anomalous pulmonary veins draining into the vena cava and a large systemic artery 1.5 cm in diameter originating from the aorta perfusing part of the lung. In addition, pulmonary pressure is elevated and with signs of right heart failure (including JVD and hepatomegaly) due to the increased pressure within the pulmonary system. Her pneumonia is treated with antibiotics.

Upon resolution of the pneumonia 2 weeks later, her pulmonary hypertension and CHF are determined to be improved enough for her to undergo surgical correction. The shunt and feeding artery are removed without complications and over time, her symptoms of CHF and pulmonary hypertension resolve.

Scimitar Syndrome (Partial Anomalous Pulmonary Venous Return):

Normal pulmonary venous circulation carries oxygenated blood from the alveolar capillaries to the left side of the heart for systemic distribution. In the Scimitar syndrome (approximately 1-3 per 100,000 births), an anomalous vein connects between the pulmonary venous circulation and systemic venous circulation which creates a left-to-right shunt that is determined by: 1) size and number of abnormal draining veins, 2) the source of venous blood flow (i.e., veins from the inferior lobe in an upright individual drains more blood than those of the superior lobe), 3) the level of pulmonary vascular resistance, and 4) the presence of other cardiovascular abnormalities. This anomalous pulmonary venous return can be either partial (PAPVR) or total (TAPVR), each with respective clinical presentations. The syndrome associated with PAPVR has been given many names in the past: pulmonary venolobar syndrome, pulmonary vascular syndrome, hypogenetic lung syndrome, and right pulmonary artery syndrome, but it is now more commonly known as "Scimitar syndrome" (1), due to the resemblance of the abnormal curvilinear pulmonary vein to a Turkish sword.

The anomalous venous connections and associated malformations are almost exclusively right-sided, with only a few reports of left-sided occurrence. The syndrome is composed of findings of: 1) An anomalous right pulmonary venous connection to the systemic venous circulation either above or below the diaphragm, most commonly to the inferior vena cava. This vein is what produces the characteristic "scimitar" shadow on X-ray. 2) Anomalous systemic arterial supply to the right lower lobe from the aorta. 3) Hypoplastic (or absent) right pulmonary artery. 4) Right lung hypoplasia with dextrocardia (the dextrocardia is typically the non-situs inversus type, and therefore, is usually a consequence of the right sided pulmonary hypoplasia). Other findings may include: a) Abnormal lobulation of the lung, b) Horseshoe lung, and c) Accessory hemidiaphragm.

Approximately 25% of presenting patients have an associated cardiac malformation, most often an ostium secundum defect (a type of ASD). Racial, sexual, and genetic predilections are largely unknown. PAPVR, was a diagnosis made at autopsy until the advent of echocardiography, cardiac catheterization, and CT/MRI scanning. The abnormal drainage of blood in the lungs can overload the right atrium and ventricle as well as decrease the preload for the left ventricle. This can lead to right ventricular dilation and decreased cardiac output. Additionally, flow from the perfusing artery stemming from the aorta may be greater than the outflow from anomalous veins, leading to increased left-sided volume loading, accelerated pulmonary hypertension, and associated symptoms of cardiac failure (2). This is not normally the case, as most symptoms arise from increased volume loading of the right heart (due to increased venous return) and pulmonary artery pressure is generally normal (3). The most common early clinical manifestation is an increased frequency of pulmonary infections.

Manifestation of clinical symptoms is dependent on the size of the shunt magnitude, expressed as pulmonary flow (Qp) to systemic flow (Qs), and can become serious when this ratio becomes >2:1. Clinical symptoms mainly manifest late in life, depending on the shunt magnitude, but occasionally they may present in childhood. These include: 1) symptoms of recurrent respiratory infections, 2) dyspnea, 3) exercise intolerance, 4) palpitations, 5) hemoptysis, 6) chest pain, 7) symptoms of associated abnormalities (e.g., ASD, pulmonary sequestration, etc.). Symptoms 2 through 6 are rare except in advanced cases where pulmonary hypertension and heart failure are present.

Physical exam reveals symptoms similar to an atrial septal defect:

1. A precordial bulge, which is a left parasternal lift due to right ventricular dilation, and possible pulsation in the 2nd intercostal space due to pulmonary artery dilation (in the absence of dextrocardia).
2. Systolic ejection murmur heard over the pulmonic area.
3. Widely split heart sound (S2) with possible normal respiratory variation.
4. This is usually a non-cyanotic condition unless there is the presence of ASD with pulmonary hypertension for shunt reversal.
5. Right-sided heart failure (include jugular venous distension, hepatomegaly, and peripheral edema).

The differential diagnosis includes: 1) atrial septal defect (clinical picture is almost indistinguishable), 2) total anomalous pulmonary venous return, 3) pulmonary sequestration, 4) ventricular septal defect.

The diagnosis of scimitar syndrome rests on demonstration of the aberrant pulmonary veins and associated abnormalities. Chest X-ray, ultrasound (echocardiography), and MRI are the choice imaging modalities for this purpose, with cardiac catheterization providing additional information in many cases. Treatment of PAPVR is symptomatic for resultant CHF, but the most definitive treatment for prevention of further complications is surgical correction of the shunt. A contraindication for surgical repair is the presence of pulmonary hypertension, which can increase the mortality rate to >50%.

A common complication of untreated PAPVR is recurrent pneumonia. The chronic, increased pressure within the pulmonary venous system can lead to pulmonary vascular and cardiac remodeling with complications of arrhythmias, right-sided cardiac failure and pulmonary vascular disease (rare). These manifest themselves to varying degrees throughout life depending on shunt size, and may be the cause of morbidity and mortality from the disease.

Pulmonary Sequestration:

Pulmonary sequestration is a segment of nonfunctioning lung tissue that usually does not associate with the tracheobronchial tree (airways within the sequestration rarely communicate with the trachea) and receives all of its blood supply from an anomalous systemic artery. The table below distinguishes Scimitar syndrome from pulmonary sequestration. The main distinguishing points are the tracheobronchial communication and the venous drainage. There are two different types of sequestrations: intrapulmonary (formerly called intralobar) and extrapulmonary (formerly called extralobar), which collectively make up approximately 6% of congenital pulmonary malformations. The development of these abnormalities is hypothesized to be from the development of a primitive lung bud from the foregut during embryonic development.

Table 1 - Comparison of Scimitar syndrome and pulmonary sequestration

	Scimitar syndrome	Pulmonary sequestration
Located within the lung	Yes	Intrapulmonary-Yes Extrapulmonary-Technically No
Arterial supply from systemic artery branch	Yes	Sometimes
Venous drainage into vena cava	Yes	Intrapulmonary-No Extrapulmonary-Yes (or right atrium or azygous vein)
Airways communicate with trachea	Yes	No
May involve the entire lung (13)	Sometimes	No
Dextrocardia (13)	Sometimes	No
ASD	Yes	No
Recurrent pulmonary infections	Yes	Intrapulmonary-Yes Extrapulmonary-Usually no
Hemoptysis	Yes	Intrapulmonary-Yes Extrapulmonary-Usually no

Intrapulmonary sequestrations are more common (75-90% of sequestrations) and are located within the lung tissue, usually in the posterior basal segment of the left lower lobe. This lesion usually occurs by itself with no associated congenital abnormalities and by definition, does not have a separate pleural covering. Communication with the tracheobronchial tree may occur via fistulas, but this is rare. 66% of lesions occur within the left lung and 99% are usually found in the posterior lung bases with venous drainage into the left atrium (4). The etiology of this lesion is unknown. Classically, intrapulmonary sequestrations do not present symptomatically until adolescence or adulthood. In fact, they are often an incidental finding on a chest X-ray performed for other reasons. When they do present clinically, it is with non-specific symptoms of cough, fever, wheezing, recurrent pulmonary infections, and rarely hemoptysis. Surgical resection of the lesion is curative and lobectomy is necessary because these are often poorly-defined masses.

Extrapulmonary sequestrations differ from intrapulmonary sequestrations in many respects: 1) the presence of a distinct and separate pleura, 2) the association with other congenital abnormalities (diaphragmatic hernia, colonic duplication, vertebral abnormalities, and pulmonary hypoplasia) (5), 3) >60% of cases present in infancy before age 6 months with a 4:1 male-to-female incidence, and 4) venous drainage is normally into the right atrium via the azygous system (11). The lesion is normally asymptomatic until associated abnormalities, infection, or shunting becomes severe. Although infants can present with cough, dyspnea, and difficulty feeding caused directly by the size of the lesion, a high degree of shunting will indirectly cause respiratory distress and CHF (7). Older children and adults usually present with chest pain and infection. Similar to intrapulmonary sequestration, if the patient is not diagnosed with an extrapulmonary sequestration during infancy because of no complications due to vascular causes (i.e., shunting), extrapulmonary sequestration will often be diagnosed as a result of an investigation for other associated anomalies. Complications are recurrent infection and hemorrhage in addition to those associated with other congenital abnormalities. Treatment is resection of the abnormality, which does not involve a lobectomy because it is a well-defined mass.

The anatomy can be further defined with the assistance of CT, MRI and angiography.

Physical examination reveals similar findings in both intra and extrapulmonary sequestrations:

1. Dullness to percussion over the lesion.
2. Decreased breath sounds over the lesion.
3. Rales may occur with a pneumonia.
4. A systolic murmur or continuous bruit associated with the arterial supply to the lesion may be present.

The differential diagnosis includes: 1) cystic adenomatoid malformation, 2) bronchogenic cyst, 3) bronchiectasis, 4) pulmonary atelectasis, 5) bronchial foreign bodies, and 6) pneumonia.

Scimitar syndrome and sequestration can both be categorized as venolobar syndromes. They both involve the lung, at least to some varying degree, and they both have cardiovascular involvement or at least the potential for cardiovascular involvement. However, while the cardinal cardiac lesion in Scimitar syndrome is partial or hemianomalous venous drainage, sequestration may not have an anomalous vascular connection. Sequestration is a disconnected or abnormally communicating bronchopulmonary mass or cyst with normal or anomalous arterial supply or venous drainage (12).

Sequestration is primarily considered to be a congenital lung malformation and because of the extra-parenchymal tissue, angiogenesis may occur causing an anomalous vascular supply. Scimitar syndrome, on the other hand, begins as a congenital cardiac malformation (usually an abnormal right pulmonary artery with or without other aberrant systemic arteries), which then causes abnormal lung development (ranging from minor abnormal bronchial branching all the way to a hypoplastic lung) and all of it is drained by the hallmark feature, an anomalous vein. In fact, bronchogenic cysts and extrapulmonary sequestrations have been found in association with Scimitar syndrome. It is because of these embryologic differences that on chest X-ray, sequestration usually appears as a cystic lesion or consolidation, while Scimitar syndrome has the characteristic Scimitar appearance with hypoplasia of the right lung.

For the above reasons, sequestration tends to be more of a condition for pulmonology specialists (pulmonology, CT, pediatric surgery), while scimitar syndrome tends to be more of a condition for cardiology specialists (cardiology, cardiac cath angiography, cardiovascular surgery).

Questions

1. What shunt fraction is considered clinically significant for the manifestation of symptoms in Scimitar Syndrome?
2. Why would you want to correct the underlying condition of scimitar syndrome early?
3. What are the complications of untreated pulmonary sequestrations?
4. What type of shunt is typical in extrapulmonary sequestration?
5. What type of sequestration is associated with a diaphragmatic hernia?
6. List three or more ways in which Scimitar syndrome differs from pulmonary sequestration.

Related x-rays

Scimitar Syndrome case: Rosen LM. Hemoptysis in a 11-Year Old: Scimitar Syndrome. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1996, volume 5, case 13. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v5c13.html

Pulmonary Sequestration case: Nakamura CT. Pulmonary Sequestration. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1996, volume 5, case 14. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v5c14.html

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Answers to questions

1. >2:1 pulmonary flow to systemic flow.
2. To prevent future complications such as: pneumonia, arrhythmia, and irreversible pulmonary hypertension (13).
3. Recurrent pulmonary infections, bronchiectasis and hemorrhage.
4. Typically, it is left-to-right venous drainage: pulmonary venous/systemic artery to the systemic venous system. Intrapulmonary sequestrations typically shunt systemic blood to the pulmonary vein (systemic artery to the pulmonary vein, which is left to left).
5. Extrapulmonary sequestration (30% are associated with diaphragmatic hernias).

6. 1) Sequestration contains bronchi that do not communicate with the trachea. 2) Two types of sequestration (intrapulmonary and extrapulmonary). 3) Dextrocardia and ASD usually accompany Scimitar syndrome. 4) Intrapulmonary sequestration venous drainage enters the left heart, while the venous drainage of Scimitar and extrapulmonary sequestration enters the right heart circulation.

Chapter VIII.9. Bronchogenic Cysts and Congenital Cystic Adenomatoid Malformations

Scott J. Sheets, DO

This is a newborn male infant born to a 25 year old G3P2 O+, rubella immune, group B streptococcus negative mother at 38 weeks gestation via spontaneous vaginal delivery. Pregnancy was complicated by ultrasound findings of mild polyhydramnios and an abnormal fetal chest finding. Apgars of 4 (-1 for respiratory effort, gag, tone and heart rate, -2 for color) and 7 (-1 for color, respiratory effort, tone) were given, at 1 and 5 minutes, respectively.

Exam: VS T 36.5, P 170, R 40, BP 80/40, oxygen saturation 90% on FiO2 of 1.00 (i.e., 100% oxygen), length 25%ile, weight 5%ile, OFC (head circumference) 50%ile. He is term in appearance, non-dysmorphic, thin appearing, in moderate to severe respiratory distress. HEENT exam is normal. His chest is slightly asymmetric, with his right hemithorax larger than the left. Suprasternal and intercostal retractions are present. Thoracoabdominal asynchrony ("belly breathing") is present. Heart is regular but tachycardic, with a grade II/VI systolic murmur best heard at the apex. Lung air exchange is moderate on the left but diminished on the right. There are no crackles or wheezing, but delayed air entry and prolonged expiration is present on the right. His abdomen is soft and non-distended, without palpable masses or hepatosplenomegaly. His extremities are symmetric, with mild acrocyanosis and no edema. Peripheral pulses are equal and within normal limits.

In the delivery room, he is given bag mask ventilation for the first minute of life with improvement in heart rate and color. He shows improved respiratory effort but remains in distress. He is intubated with a 3.5 endotracheal tube and transported to the NICU where he is placed on mechanical ventilation. A nasogastric tube is passed to decompress the stomach. A chest radiograph demonstrates cystic lesions occupying much of the lower right lung field. The mediastinum is shifted toward the left. One of the residents thinks that this is bowel in the chest (based on its appearance) with an associated diaphragmatic hernia. But the neonatologist cautions that a diaphragmatic hernia on the right is unusual. An emergent CT scan shows several small cysts within the right lower lobe with a prominent large cyst compressing the right mainstem bronchus, upper and middle lobes, and shifting the mediastinum. The left lung is small (slightly hypoplastic). Serial chest radiographs show that the lesions are stable over the first 24 hours. A cardiothoracic surgeon is consulted. The child is taken to surgery on the second day of life. Intraoperatively, it is apparent that the lesions are contained within the right lower lobe, so this lobe is resected. The pathologic examination of the resected lobe confirms a type I congenital cystic adenomatoid malformation (CCAM).

Immediately post-operatively, ventilation is improved. Chest radiographs show that the mediastinum has returned to midline, the right upper and middle lobes compensate to fill the hemithorax. The left lung, now no longer compressed, shows normal development. Over the following weeks, ventilation and oxygenation improve, and the infant is converted from high frequency oscillatory ventilation (HFOV) to a conventional mechanical ventilator with an emphasis on minimizing barotrauma. Breath sounds are symmetric. The child is weaned from the ventilator, and over time, he no longer requires supplemental oxygen.

Congenital malformations of the airways and lungs make up approximately 10-15% of all malformations and are often found with other congenital anomalies (18-20%). The following review includes a description of two of the more common lung malformations: bronchogenic cysts and congenital cystic adenomatoid malformations (CCAM). The vast majority of foregut cysts found in infancy are bronchogenic cysts (1).

Bronchogenic cysts are one type of a foregut cyst (a closed epithelial-lined sac developing abnormally from both the upper gut and respiratory tract). A bronchogenic cyst is thought to develop as a diverticulum of the primitive foregut. Since most form very early, usually 4-8 weeks gestation and before the development of distal airways, they rarely connect to a normal bronchus. Most are right sided, midline and in close proximity to the tracheobronchial tree. On rare occasions they can separate the connection to the airway and migrate to the periphery, parahilar area or even below the diaphragm. Five categories have been described by location: 1) paratracheal 2) carinal 3) para-esophageal 4) hilar and 5) other. They may contain normal tracheal tissue including mucus glands, elastic tissue, smooth muscle and cartilage. They are lined with ciliated epithelium. They range from 2-10 cm in diameter. The cyst may contain serous (with the consistency of water) or proteinaceous fluid (2,3).

Congenital cystic adenomatoid malformation (CCAM) is a congenital bronchopulmonary anomaly resulting from a maldevelopment of the lung bud in the fetus (1). CCAMs are a defect of non-cartilage containing terminal respiratory structures, resulting from an abnormality occurring in the mid to late stages of lung development. Although these lesions are frequently described as hamartomatoid, they are not true hamartomas because skeletal muscle can be found in the wall of the cyst. The following is a list of distinguishing features that define the group: 1) absence of cartilage, 2) absence of bronchial tubular glands, 3) presence of tall columnar mucinous epithelium 4) increased production of terminal bronchiolar structures without alveolar differentiation 5) increased enlargement of the affected lobe (4).

There are at least 4 subtypes described, although type 0 is not compatible with life. The different subtypes are primarily described by their gross physical appearance, but they also differ by their variations in microscopic findings and embryologic origin. Each subtype has differing prognostic indications. Type 0 (most rare) is tracheobronchial in origin, with small, firm and granular lungs. Microscopically there are bronchial-like structures separated by mesenchymal tissue.

Type I (macrocystic subtype) is the most frequent variant (60-70%). It has bronchial-bronchiolar origins and at least one prominent cystic structure, although several smaller cysts may also be present. Type I malformations have little adenomatoid component and are mainly lined by ciliated pseudostratified epithelium. They contain cysts interspersed with bronchiolar and alveolar tissue.

Type II (microcystic subtype) is the next most frequent variant (15-20%). Smaller cysts with ciliated cuboidal or columnar epithelium are the dominant feature. It has a mix of cystic and adenomatoid components and is bronchial in origin. Between the cysts are distended respiratory bronchioles and alveolar tissue. These may also contain skeletal muscle. This subtype is associated with a higher incidence of other anomalies.

Type III (solid subtype) is rare (8-10%). It is a bulky lesion, with thin walled cysts. Type III is almost entirely adenomatoid in make-up. It is an airless mass of bronchiolar elements, lined by patchy ciliated cuboidal epithelium mixed with alveolar elements.

Some describe Type IV (10-15%) as a large cystic lesion in the periphery of the lung, believed to be of acinar origin. Others do not describe this subtype and incorporate it into the others. These cysts are lined by flattened pneumocytes (5-6).

The clinical manifestations of a bronchogenic cyst depend on size, location and whether there is a communication with the airway or esophagus. They can present with fever, dyspnea, stridor, chronic cough, chest pain, dysphagia, cyanosis, crackles, wheezing, pulmonary sepsis or suppuration of the cyst, respiratory distress or swelling. Bronchogenic cysts can present as a draining sinus, typically located in the suprasternal notch or supraclavicular area. Superior vena cava syndrome has been seen. They are asymptomatic in up to 30% (7).

CCAMs present early in the newborn period with respiratory distress (dyspnea, tachypnea, grunting, retractions or cyanosis) in approximately 75% of cases. The mass lesion comprised of growing cysts can compress the surrounding structures. Compression during development of the surrounding lung can cause pulmonary hypoplasia, maldevelopment of the heart and great vessels (may cause fetal hydrops), or hypoplasia of the airways (can lead to respiratory distress). For those who do not present in the newborn period, they may present at any point in life. The lesions can develop infections, as they do not have normal clearance mechanisms, leading to recurrent pulmonary sepsis. A higher percentage of these lesions are being diagnosed or suspected prenatally by ultrasound.

On chest radiographs, bronchogenic cysts usually appear as a spherical or ovoid mass close to the carina or mainstem bronchus. CCAMs appear as obvious solid or cystic masses with or without pleural effusion. Diagnosis is suspected by CXR, CT, MRI, endoscopy or fluoroscopy, but is confirmed by pathologic evaluation of tissue.

Bronchogenic cysts are most commonly confused with the other main type of foregut cysts, esophageal duplication cysts. The rest of the differential diagnosis includes cystic hygroma, thymoma, thyroid tumors, dermoid cyst, congenital lung emphysema, pulmonary abscess, pneumatocele, thyroglossal duct cyst, bronchial duct cyst, teratomas, necrotic cervical lymphadenopathy, neurogenic tumors, primary malignancy, lipoma and leiomyoma.

CCAMs are most frequently mistaken for congenital diaphragmatic hernia (since the cysts can resemble bowel gas in the chest on CXR) but the differential includes simple parenchymal cysts, infections, sequestration, mesenchymal cystic hamartomas, mesothelial cysts or cystic lymphangiectasis (8-10).

The treatment of choice in all forms of bronchogenic cysts and CCAMs is surgical excision, which also provides confirmation of the diagnosis. Bronchogenic cysts may rupture into a bronchus or pleura, bleed profusely or become infected. These complications can cause problems at the time of surgical excision or produce sudden death. If they have already been secondarily infected, the excision may have to be delayed until antibiotic treatment can clear the area of infection. If resection is not complete, recurrence is possible. For CCAM, early resection will allow for compensation of lung growth from the remaining sections, and prevents secondary infections, that otherwise commonly occur.

Left untreated, bronchogenic cysts may develop malignancy including rhabdomyosarcoma, leiomyosarcoma, or anaplastic carcinoma. In one study of symptomatic infants, there was 100% mortality without surgery. Of those infants undergoing surgery, mortality rates were reported to be 0-14%. The prognosis for those surviving surgery was good. In some, residual tracheomalacia or bronchomalacia may be present.

CCAM Type 0 is not compatible with life and these infants are usually stillborn, or spontaneously aborted. Type I lesions have the best prognosis. For those surviving surgical resection, the prognosis is excellent with compensatory lung growth of the remaining segments. Type II has a worse overall outcome compared to Type I, largely because of the other associated anomalies. Type III has a poor prognosis, due to the degree of hypoplasia frequently seen in the other lung segments. If untreated, there is also a potential for malignant transformation in CCAM.

Another important consideration for those patients with either type of lesion is air travel, when transport to a tertiary care center is needed for further management. The cystic lesions have been known to expand 30% in size during flight, which may cause a significant mass effect and further compression of vital structures. Care must be taken to avoid significant pressure changes by flying at low altitudes, or in special aircraft capable of pressurization to sea level.

Questions

1. Which of the following lesions contain no cartilage?
    a. Bronchogenic cyst
    b. Congenital cystic adenomatoid malformation
    c. Both of the above
    d. Neither of the above

2. Which of the following lesions is a form of foregut cyst?
    a. Bronchogenic cyst
    b. Congenital cystic adenomatoid malformation
    c. Both of the above
    d. Neither of the above

3. Which of the following lesions is usually associated (has a direct connection or communication) with the tracheobronchial tree?
    a. Bronchogenic cyst
    b. Congenital cystic adenomatoid malformation
    c. Both of the above
    d. Neither of the above

4. In symptomatic lesions, both CCAM and bronchogenic cysts should be resected. In which of the following, can asymptomatic lesions be followed clinically?
   a. Bronchogenic cyst
   b. Congenital cystic adenomatoid malformation
   c. Both of the above
   d. Neither of the above

5. Which of the following lesions frequently cause symptoms by mass effect?
   a. Bronchogenic cyst
   b. Congenital cystic adenomatoid malformation
   c. Both of the above
   d. Neither of the above

6. Which type of CCAM has the best prognosis?
   a. Type 0
   b. Type I
   c. Type II
   d. Type III
   e. Type IV

7. Which type of CCAM is most common?
   a. Type 0
   b. Type I
   c. Type II
   d. Type III
   e. Type IV

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Answers to questions

1.b, 2.a, 3.b, 4.d, 5.c, 6.b, 7.b

Chapter VIII.10. Congenital Airway Problems
Winona K. Lee, MD

This is a 4 week old male who has been brought to your office with a one week history of "noisy breathing." His parents note that his noisy breathing is worse when they lay him down or with crying. It is most noticeable when he takes a breath in. There has been no history of fever, coughing, runny nose, change in his cry, apnea, or feeding difficulties. He has been gaining weight appropriately. Prenatal course was uneventful and he was delivered at 38 weeks gestation by spontaneous vaginal delivery without complications. Family History is unremarkable.

Exam: VS T 37.0, P 120, RR 48, oxygen saturation 98% in room air. Weight and height are at the 50%ile. He is alert, active, in no acute distress. There is audible inspiratory stridor noted in the supine position, which is improved with extension of his neck. His anterior fontanel is soft and flat. His eyes and ears are normal. No nasal flaring is visible and his nares appear patent. His throat shows no erythema or lesions. His lips are moist and pink. There are no retractions or pectus abnormalities. His lungs are clear to auscultation throughout once the stridor clears with airway repositioning (no wheezes or rales). Aeration is good. He has noisy referred upper airway sounds when he is supine with his neck flexed. His heart is regular without murmurs. His color, perfusion, capillary refill and pulses are good.

He is referred to ENT for a flexible fiberoptic laryngoscopy, which confirms the diagnosis of mild laryngomalacia. His status is monitored clinically. He continues to feed well and gain weight appropriately. All his symptoms resolve by 18 months of age.

Laryngomalacia

Laryngomalacia is the most common congenital anomaly of the larynx. It represents 60% of all congenital laryngeal anomalies (1). Males are affected twice as often as females. It is generally self-limiting, however, severe cases of laryngomalacia can lead to failure to thrive and life-threatening apnea (2).

The exact etiology is unclear, however, theories include maldevelopment of the cartilaginous structures of the airway and immature neuromuscular control. The epiglottis is derived from the 3rd and 4th brachial arches. An overgrowth of the 3rd arch results in an elongated and laterally extended epiglottis (1). Neuromuscular immaturity may contribute to the prolapse of the arytenoids observed in laryngomalacia; however; there is no increase in the incidence of laryngomalacia in premature infants with classic hypotonicity (1).

Symptoms of laryngomalacia are typically absent at birth, arising at 2 to 4 weeks of age. Common symptoms include inspiratory stridor, which is worsened with supine position and with agitation or excitement (3). Feeding difficulties, exacerbated by gastroesophageal reflux, may occur due to the increased negative intrathoracic pressure created by a partially obstructed airway (2). Patients have a normal cry and rarely present with respiratory distress or cyanosis. Rare complications include chest deformities, obstructive apnea, and failure to thrive (1).

The classic history will guide one to the diagnosis of laryngomalacia; however, diagnosis is confirmed by flexible laryngoscopy while the patient is awake (3). Laryngoscopy typically reveals an elongated and laterally extended (omega shaped) epiglottis that falls posteriorly on itself on inspiration. Visualization also reveals inward collapse of the aryepiglottic folds (cuneiform cartilages) on inspiration and bulky arytenoids that prolapse on inspiration (1).

Management is expectant with simple reassurance for parents. Patients are observed for adequate growth. Symptoms of gastroesophageal reflux should be monitored since this can aggravate symptoms and can be improved with anti-reflux precautions. In patients with failure to thrive or obstructive apnea, surgical interventions such as epiglottoplasty (dividing the aryepiglottic folds and trimming the epiglottis) may be required (2).

Vocal Cord Paralysis (also known as Vocal Fold Paralysis)

The second most common congenital anomaly of the larynx is vocal cord paralysis, accounting for 20% of laryngeal lesions. The paralysis can be unilateral or bilateral. In general, bilateral paralysis is usually due to a central nervous system problem, while unilateral paralysis is typically caused by an injury to the peripheral nervous system (2). Specific causes of vocal cord paralysis include meningomyelocele with Arnold-Chiari malformation, hydrocephalus, birth trauma, and surgical trauma (4).

Infants with vocal cord paralysis may present at birth or within the first few weeks of life. Symptoms include a weak or breathy cry, noted typically in unilateral vocal cord paralysis. Patients may also present with inspiratory or biphasic stridor, aspiration or feeding difficulties, and occasionally respiratory compromise (3).

The diagnosis of vocal cord paralysis can be made at the bedside with direct visualization of the vocal cords using a laryngoscope (direct laryngoscopy), but is confirmed by rigid endoscopy under anesthesia while the patient is breathing spontaneously. Alternatively, flexible laryngoscopy while the patient is awake to assess vocal cord mobility can be used. Imaging may be utilized to rule out associated CNS lesions (4).

Initial management includes stabilization of the airway and support for feeding and nutrition (3). In most cases of unilateral vocal cord paralysis, no intervention is needed since compensation by the opposite vocal cord occurs over time and most cases resolve within the first few weeks of life. In bilateral vocal cord paralysis, tracheostomy is generally required to stabilize the airway. Bilateral vocal cord paralysis secondary to a neurological problem often improves once the neurological problem is addressed. In cases of idiopathic bilateral vocal cord paralysis, symptoms may spontaneously resolve by age of 2. If not, it is unlikely to do so. Surgical methods have had moderate success in improving the airway and promoting decannulation (removal of tracheostomy) by age 4 to 5 years (2).

Congenital Subglottic Stenosis

Congenital subglottic stenosis is the third most common congenital anomaly of the larynx. It accounts for 15% of all cases. Males are affected twice as often as females (5). Congenital subglottic stenosis is usually associated with a small or malformed cricoid cartilage with or without thickening of the underlying submucous layer.

Patients with subglottic stenosis may be asymptomatic until an upper respiratory infection causes further narrowing of the airway. The patient may present with biphasic stridor and a barking cough may be noted. Many patients are diagnosed with recurrent croup prior to a final diagnosis of subglottic stenosis. With severe subglottic stenosis, patients will present with dyspnea and marked suprasternal and subcostal retractions. The patient's cry remains unaffected (2).

A history of recurrent croup may support the diagnosis of congenital subglottic stenosis. Subglottic narrowing may be noted on plain lateral and AP x-rays and the diagnosis is made with rigid bronchoscopy. The length and diameter of the stenosis is measured and

congenital subglottic stenosis is diagnosed when the lumen diameter is less than 4 mm in a term infant or less than 3 mm in a preterm infant (1).

In the majority of patients with subglottic stenosis, respiratory problems resolve with growth of the child. However, endotracheal intubation and tracheostomy may be needed in patients with significant airway compromise. Decannulation by age 3 to 4 years is usually possible when the subglottic space widens. Laryngeal reconstruction to enlarge the lumen of the stenotic airway has proven successful in severe cases of congenital subglottic stenosis (4).

Tracheomalacia

In tracheomalacia, the trachea lacks firmness, causing the anterior and posterior walls to come together during respiration, decreasing the tracheal lumen. Tracheomalacia occurs in 2 forms: primary and secondary. Primary tracheomalacia is rare and is caused by a congenital deformity of the supporting tracheal rings. Secondary tracheomalacia is due to external compression from lesions such as vascular anomalies (e.g., vascular ring), tumors or hemangiomas. It can also result from surgical intervention such as tracheoesophageal fistula repair (5).

Patients with tracheomalacia can present with inspiratory or expiratory stridor, wheezing, and a barking cough. Dramatic "dying spells", in which the patient undergoes reflex apnea, progressing to cardiac arrest can also occur. Patients can also present with recurrent pneumonitis secondary to chronic obstruction and difficulty clearing bronchial secretions (5).

Direct endoscopy is the only reliable method to diagnosis tracheomalacia. Both types of tracheomalacia are typically self-limited, but in severe cases a tracheostomy may be needed to stent the trachea during development. In the secondary form, correction of the underlying lesion to alleviate external compression is associated with a good outcome (3).

Congenital airway anomalies must be considered when evaluating stridor of infancy. The key is to separate life-threatening conditions from those which are self-limited. With a thorough history and physical examination, one can establish the initial diagnosis, make the appropriate referral to the ENT specialist, and support the infant until a diagnosis is confirmed.

Questions

1. What is the most common cause of laryngeal anomalies in infants?

2. Classically, the stridor in laryngomalacia is:
   a) inspiratory b) expiratory c) biphasic

3. The secondary form of tracheomalacia is usually due to:
   a. a congenital deformity of the supporting tracheal rings.
   b. an extrinsic compression such as a vascular anomaly.
   c. surgical intervention such as tracheoesophageal fistula repair.
   d. b and c.
   e. all of the above.

4. Anatomically, congenital subglottic stenosis is usually associated with what other airway malformation?

5. As the second most common laryngeal anomaly, vocal cord paralysis accounts for what percentage of laryngeal lesions?

6. A child with a diagnosis of recurrent croup may suggest which airway anomaly?

7. Most cases of laryngomalacia resolve by what age?
   a. 6-12 months old
   b. 12-18 months old
   c. 18-24 months old
   d. 24-36 months old

8. In general, bilateral vocal cord paralysis can be attributed to a _____nervous system problem, while unilateral vocal cord paralysis is usually caused by an injury to the ___nervous system.

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Answers to questions

1. Laryngomalacia
2. a. inspiratory
3. d. b and c
4. small or malformed cricoid cartilage
5. 20%

6. congenital subglottic stenosis
7. c. 18 to 24 months old
8. central, peripheral

Chapter VIII.11. Sleep Disorders
Sze Mei Chung

This is a 4 year old boy who is brought to the office by his single mother with a chief complaint of screaming at night for about a year. He has been in good health otherwise with no recent history of otitis or respiratory infection. There is no history of nervous system malformation, seizure, or sleep walking. According to his mother, she would hear a chilling scream, rush to her son, and find him sitting up in bed, sweating with a glassy stare. There is no response when she talks to him, and when she tries to hug him, he usually resists. But when her son does answer after more vigorous shaking, he seems confused and disoriented. This mostly happens approximately at midnight, 2-3 hours after his bedtime. In the morning he would seem fine and not remember having any nightmares or screaming.

Exam: VS T 37.5, P 90, R 24, BP 92/53. He is a shy, healthy looking boy in no apparent distress. His examination is normal.

He is referred to a sleep specialist who assesses the boy as having sleep terrors. His mother is taught to help avoid stresses and fatigue for her son during the daytime. Short naps of 30-60 minutes in late afternoon are suggested. His mother is told that diazepam may be prescribed if his problem worsen, but most of the time, children will outgrow this disorder.

When children present with sleep problems, a careful history should be taken (1). This includes age of onset, patterns of daytime sleepiness and napping, questions about snoring and apnea, sleep related behaviors such as talking and head banging, psychiatric assessment regarding separation anxiety and nightmares, relevant medical/neurological conditions such as headaches, and mental retardation, and family histories of sleep disorders.

Studies such as polysomnography (PSG), limb actigraphy, and multiple sleep latency test (MSLT) can be useful in diagnosing the cause of the sleep problem. PSG includes measurements of eye muscle movement, EMG, EEG, EKG, respiratory measurements (i.e., thoracic/abdominal excursion, air flow, and oximetry) during sleep. MSLT is based on PSG that objectively measures daytime sleepiness by recording sleep onset and type of sleep with 5 regularly spaced daytime naps. Limb actigraphy uses an instrument resembling a wrist watch that detects body movements continuously for 3 days. However, for disorders that are more sporadic, PSG may not be definitive. In cases of arousal disorders (sleep terror and sleep walking), having the parents record the episodes on a video camcorder may be more useful. Sleep disorders can be categorized into dyssomnias, parasomnias, and sleep disorders due to medical or psychiatric conditions (2).

Normal sleep is composed of rapid-eye-movement (REM) and non-REM (NREM) types. REM sleep is the dreaming stage of sleep, whereas NREM is sleep that is further divided into 4 stages depending on the PSG readings. Stage 1 NREM sleep can be defined as "drowsiness" where alpha waves of wakefulness are replaced by theta waves in EEG, and during which slow, rolling eye movements are observed with slightly decreased tonicity in EMG recordings. This is followed by K complexes characteristic of Stage 2 NREM sleep. Stages 3 and 4 of NREM sleep are known as slow-wave sleep where delta waves on EEG dominate. In stage 3, delta waves are present in 20-50% of the EEG, while in stage 4, delta waves are present in >50% of the EEG (3,4).

Dyssomnias are disturbances of normal sleep or sleep rhythm pattern. This disorder is characterized by not enough, too much, or inefficient sleep. Dyssomnias can be broken down into 3 categories: intrinsic dyssomnias, extrinsic dyssomnias, and circadian dyssomnias (5).

Intrinsic dyssomnias are due to causes within the body and include breathing related sleep disorders (sleep apnea) and narcolepsy. Sleep apnea occurs when air flow is completely stopped and is diagnosed when there are 5 apneas or 10 apnea-hypopnea episodes per hour of sleep. Compared to apnea, hypopnea is shorter duration of decreased ventilation. However, the precise criteria for defining hypopnea is controversial. In general, hypopnea can be thought of as episode where airflow is reduced by one-half to two-thirds (6). Audio tape recording of the episode can also aid in the diagnosis. Apnea by itself is not a problem except when it exceeds 10 seconds in duration. Patients are not aware of their apneas but sometimes do wake up with a choking feeling.

There are 3 types of sleep apnea: central, obstructive, and mixed sleep apnea. Central apnea results from no respiratory effort because of brainstem respiratory neuronal immaturity, which is commonly seen transiently in premature babies and newborns. Obstructive sleep apnea is caused by airway obstruction. In young children, the obstruction is most often due to enlarged tonsils and adenoids and not usually from severe obesity (2). Surgical removal of the enlarged tonsils and adenoids may be curative. Apnea is accompanied by increased thoracic and diaphragmatic respiratory effort without air exchange due to upper airway obstruction. Mixed sleep apnea combines features of both central and obstructive causes.

Because of apneic episodes, the patient experiences many short arousals to restore adequate oxygenation. These arousals can severely interrupt the sleep cycle. Thus, symptoms of daytime sleepiness and inattention are evident. In toddlers, growth retardation similar to that seen in failure to thrive can be observed possibly associated with disruption of growth hormone secretion during fragmented sleep.

A related disorder in children is central hypoventilation syndrome (or Ondine's curse) caused by central chemoreceptor impairment leading to nocturnal seizures and hypoxia (7). Treatment includes mechanical ventilation or phrenic nerve pacing (3). Other hypoventilation syndromes include Pickwickian syndrome (named for the Joe, the fat boy in Dickens' Pickwick Papers), a rare complication of extreme obesity characterized by hypersomnolence with apneic pauses, polycythemia, and eventual right-sided heart failure (8,9). Likewise Prader-Willi syndrome can also cause obstructive sleep apnea (10). Prader-Willi syndrome is a genetic disorder due to deletion of q12 in the long arm of the paternal chromosome 15. Initially, the infant presents with hypotonia followed by rapid weight gain after 1 year of age leading to morbid obesity (11,12, 13). In cases of Pickwickian and Prader-Willi syndromes, reducing weight is of primary importance and should be achieved as fast as is feasible (14). Examples of other conditions predisposing to obstructive sleep disorders are Down syndrome, craniofacial anomalies, mucopolysaccharidoses, and neuromuscular disorders.

Narcolepsy is the only REM sleep dyssomnia. Its peak incidence (<1%) is between 15 to 25 years of age (5). Its etiology is unknown, but there is strong genetic predisposition (with HLA-DR2 and HLA-Dqw1, and first degree relatives of affected individuals

being eight times more likely to suffer from REM sleep disorders) (2). In severe cases, narcolepsy consists of a clinical tetrad: 1) sleep attack characterized by an irresistible urge to sleep for 5-20 minutes, 2) cataplexy (or an intrusion of REM atonia while awake), manifested as an abrupt muscle tone loss (total loss of whole body muscle tone) triggered by strong emotions such as anger (the patient may be fully awake, but is unable to move), 3) sleep paralysis, which is REM atonia at sleep-wake transition (when falling asleep or waking up) when the patient briefly cannot move, and 4) hypnagogic hallucinations in which dreams continue into the waking state resulting in illusions or hallucinations.

PSG is required for the diagnosis of narcolepsy. Treatment is symptomatic. Regular sleeping and rising times are recommended with scheduled naps 2-3 times a day. Psychosocial counseling and support are important as narcolepsy is a debilitating life-long condition once diagnosed. Stimulants maybe indicated by excessive daytime sleepiness. For treating cataplexy, tricyclic antidepressants and clomipramine have been successful.

Unlike intrinsic dyssomnias, extrinsic dyssomnias are due to external causes and includes protodyssomnias (an inability to fall asleep and stay asleep) of infancy and insomnias of childhood (2). Examples include night waking, and difficulty falling asleep. Predisposing factors include previous behavior reinforcement patterns, child temperament (e.g., ADHD), poor nutrition, milk allergy, marital dispute, and physical discomfort. Currently, it is not known whether these protodyssomnias progress to true dyssomnias later on (2). Individualized bedtime habits such as reading or playing a quiet game can also help.

Circadian rhythm dyssomnias are characterized by inappropriate timing of sleep. This is more likely to occur in adolescence when bedtime is pushed back later. The teenager then tries to make up for the lost sleep by sleeping long periods during the weekend. Thus, this irregular sleep pattern leads to biologic clock disruption over time resulting in circadian rhythm dyssomnias characteristic of delayed sleep phase syndrome. This syndrome presents with an inability to sleep and wake at a customary time, excessive daytime sleepiness, and many naps with no difficulty in maintaining sleep once asleep. Diary/sleep logs reveal irregular sleep times, and MSLT is helpful in quantifying sleep debt. Treatment consists of eliminating sleep debt and reinforcing appropriate bedtime and rise time. When supportive or behavioral therapy fails, chronotherapy is indicated. Chronotherapy (phase delay treatment) allows the biological clock to reset by delaying sleep and rising times by 2 hours each day until the time of sleep onset is shifted back to a more reasonable hour.

Unlike dyssomnias in which the sleep process is disrupted, parasomnias represent behavioral intrusions upon ongoing sleep. These behaviors are caused by CNS arousal, especially activation of motor and autonomic components. Parasomnias are more likely to occur in males than females, and a patient suffering from one parasomnia is likely to exhibit another. For example, a child with sleep terror may also experience sleepwalking. Parasomnias can be divided into the following categories: arousal disorders, sleep-wake transition disorders, REM parasomnias, and other miscellaneous parasomnias.

Arousal disorders include sleep terror disorder and sleepwalking. Arousal disorders occur at transition from NREM stage 4 to REM sleep, which usually occurs 1-3 hours after sleep onset. Problems occur when this normally smooth transition is characterized by autonomic activity. In sleep terror, the child typically sits up, screams, and has a glassy, unseeing gaze associated with autonomic symptoms of palpitations, diaphoresis, and irregular breathing. This lasts for about 1 to 5 minutes until the child calms down and continues to sleep. A child in this condition is difficult to wake up and appears disoriented and confused when he does awaken. Unlike nightmares, the child does not recall the incident or any dreams in the morning (15,16). Sleepwalking may accompany sleep terrors and can be dangerous. The body movements that occur during sleepwalking are purposeless and uncoordinated. Locking the doors and windows and installing alarms that alert the parents when the child rises from bed are some of the safety measures (17).

Sleep lab studies may not be helpful since arousal disorders occur sporadically. Rather, having the parents videotape the episode of attack can be more diagnostic. As daytime stress and fatigue are known precipitators of arousal disorders, they should be avoided. Short naps can reduce NREM stage 4 sleep which reduces the likelihood of sleep terrors. Benzodiazepines can reduce numbers of attacks but drug tolerance develops. In severe cases or if the onset occurs in adolescence, it is important to rule out sleep-related seizures.

Sleep-wake transition disorders occur at transitions between sleep and waking. Examples of this category of parasomnias are rhythmic movements, nocturnal leg cramps, and sleep talking. Rhythmic movements include head banging, sleep starts (defined as sudden muscle jerks at sleep onset that may involve the limbs, neck, or entire body), and body rocking that usually occurs at sleep onset for <15 minutes duration. Prevalence decreases with age, and generally, measures to prevent self injury are sufficient.

Nightmares are by far the most common of REM parasomnias. Onset occurs at 3-6 years of age and up to 50% of this age group experience nightmares severe enough to worry their parents. Nightmares are terrifying arousals from REM sleep associated with anxious dream reports. Unlike sleep terrors, a child with nightmares can recall the event well in the morning. Also, nightmares typically take place in the last third of sleep when REM sleep dominates compared to sleep terror occurrences in the first 1-3 hours after sleep onset (NREM stage 4) (18). Treatment of nightmares mainly focuses on providing comfort and reassurance during the incident and reducing daytime stress. Withdrawal from certain medications such as beta-blockers and other drugs that suppress REM sleep (including tricyclic antidepressants and alcohol) can also trigger nightmares.

There are many other miscellaneous parasomnias. But the two most common ones in children are sleep bruxism and sleep enuresis. Sleep bruxism is stereotypic mouth movements in sleep that results in teeth grinding. Dentists are usually the first one to notice this problem. Bruxism is strongly related to stress and strained emotions. Management consists of dental interocclusal appliances (to prevent enamel wear), behavioral therapies, and night alarms. Sleep enuresis, or bed wetting, is diagnosed in the absence of urologic, medical, or psychiatric conditions in children after 5 years of age.

In studying sleep in the younger age groups, one should consider the age related differences in sleep stages and their implications. During the 1st year of life, REM sleep associated with arousals is dominant. Thus, infants are more likely to suffer from dyssomnias with sleep maintenance. During the preschool years, NREM stages predominate. Because NREM arousal parasomnias more often occur at the transition from deep to REM sleep, these sleep problems are more commonly seen in the preschool to primary school years and tend to disappear by teenage years. Adolescents, on the other hand, are more likely to be sleep deprived due to increasing workloads from school, sports, and social activities and events. The disruption of regularly sleep schedules and decrease in total amount of sleep predispose them to circadian rhythm dyssomnias.

Here is a summary outline of the sleep disorders discussed so far:

A. Dyssomnias
   1. Intrinsic dyssomnias
      a. Breathing related sleep disorder
         1) Central (prematurity, Ondine's curse, etc.)
         2) Obstructive (large tonsils/adenoids, Pickwickian, Prader-Willi, etc.)
         3) Mixed
      b. Narcolepsy
   2. Extrinsic dyssomnias
      a. Infant protodyssomnia
      b. Childhood insomnias (psychosocial and physiologic stress)
   3. Circadian rhythm disturbances (adolescents)

B. Parasomnias
   1. Arousal disorders
      a. Sleep terrors
      b. Sleep walking
   2. Sleep-wake transition phenomena
      a. Sleep talking
      b. Nocturnal leg cramps
      c. Rhythmic movement disorders
   3. REM parasomnias
      a. Nightmares
   4. Miscellaneous parasomnias
      a. Sleep bruxism
      b. Sleep enuresis

Disturbed sleep related to neurologic disorders can be due to diverse causes such as headaches, seizures, mental retardation, and cerebral degenerative disorders. The severity of the sleep problem is correlated to the extent of the neurologic conditions. Psychiatric problems can also lead to night time wakings, nightmares, or difficulty going to sleep. Examples are emotional trauma, stress, separation anxiety, attention deficit hyperactivity disorder, conduct disorder, and Tourette's syndrome. In older children, generalized anxiety disorder and major depression can play a role also. Thus, in assessing sleep disorders, the physician must distinguish between primary causes and sleep disturbances related to other medical or psychiatric disorders.

Questions

1. Which of the following helps to distinguish sleep terror from nightmares?
   a. Child does not recall the incident in the morning.
   b. Child is diaphoretic upon awakening.
   c. Common sleep disorder to occur in childhood.
   d. None of the above.

2. In which of the following cases would PSG (polysomnographic recordings) not be as helpful?
   a. Narcolepsy
   b. Sleep terror
   c. Sleep apnea
   d. a & b

3. Which of the following is NOT a primary sleep disorder?
   a. Tourette's syndrome
   b. Sleep bruxism
   c. Rhythmic movement disorder
   d. Protodyssomnia of infancy

4. Describe the clinical tetrad of narcolepsy?

5. Describe at least two causes of obstructive sleep apnea and two causes of non-obstructive sleep apnea?

6. Circadian rhythm dyssomnias typically occur in which age group?

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Answers to questions

1.a, 2.b, 3.a

4. Sleep attack, cataplexy, sleep paralysis, hypnagogic hallucinations

5. Obstructive: Tonsillar enlargement, Prader-Willi syndrome, Pickwickian. Non-obstructive: Prematurity, Ondine's Curse.

6. Adolescence

Chapter VIII.12. Sudden Infant Death Syndrome (SIDS)

Mary Elaine Patrinos, MD

A 2-1/2 month old male infant presents to the emergency department via ambulance in full arrest. The baby has been well until 3 days prior when he developed a mild upper respiratory tract infection. On the day he presents to the ED, his appetite has been somewhat decreased, but there are no other symptoms. His mother left him with the sitter in the morning before going to work. After a feeding, the sitter put him down to sleep. She checked him approximately 30 minutes later, because of the recent URI, and found him apneic, pale, mottled, and limp. She attempted CPR briefly and called 911. CPR and resuscitation standing orders were implemented in transport. The patient arrives intubated with an intraosseous infusion. Two doses of epinephrine have been administered so far.

Birth History: Born at term with a birth weight of 3.3 kg (7 lbs. 4 oz). Uncomplicated perinatal and neonatal course; normal spontaneous vaginal delivery. Discharged from the hospital with his mother on day of life 3.

Exam: VS T 35 degrees C (95 degrees F), pulse and respirations with CPR, BP 100/50 with CPR. The infant is pale, mottled and cyanotic.

Clinical Course: CPR and resuscitation drug protocols are continued; however after 30 minutes of resuscitation, there is no response to these measures and the infant is pronounced dead.

Sudden infant death syndrome (SIDS) is defined as the sudden death of an infant (<1 year of age) that remains unexplained after review of the clinical history, a complete autopsy (including skeletal survey, metabolic and infectious disease assessment, and toxicology investigation), and examination of the death scene. It is a diagnosis of exclusion often affecting previously healthy infants. Despite a recent decline in SIDS deaths, it remains the number one cause of post-neonatal infant mortality with an incidence of 0.7-0.8 per 1000 live births (1). The incidence peaks between 2 and 4 months of age with 90% of SIDS deaths occurring before the age of 6 months. The etiology is unknown, however a number of risk factors have been identified which include: prone sleep position, sleeping on a soft surface, co-sleeping, maternal smoking, overheating, lack of adequate prenatal care, young maternal age, prematurity and/or low birth weight, and male sex. African Americans and American Indians have SIDS rates which are 2-3 times the national average (2).

Many mechanisms have been proposed for SIDS, the most popular of which has been the apnea hypothesis. This theory assumes that infants with documented cardiorespiratory events are at increased risk of SIDS. It was this theory that prompted and has, to some extent, continued to support the long-standing use of home apnea monitors for certain high-risk patient populations such as preterm infants, infants with apparent life threatening events (ALTE), and siblings of SIDS victims. However, a recent study examining cardiorespiratory events in healthy term infants versus those at increased risk for SIDS demonstrated that preterm infants had the largest number of extreme cardiorespiratory events (apnea of at least 30 seconds and bradycardia of <60 bpm for >10 seconds) (3). By 43 weeks postconceptional age, the relative risk of having an extreme event was no longer significant in the preterm versus the full term group. Given the fact that the

incidence of SIDS peaks well beyond 43 weeks postconceptional age, it was concluded that prolonged apnea and significant bradycardia were not likely to be immediate precursors to SIDS.

It is currently believed that many mechanisms contribute to SIDS. A leading hypothesis maintains that many of these infants have an immature or abnormal arousal response. Postmortem examinations of the brainstems of infants dying of SIDS have revealed hypoplasia or decreased neurotransmitter binding of the arcuate nucleus. The arcuate nucleus is thought to be involved with the hypercapnic ventilatory response, chemosensitivity, and blood pressure regulation (2). Infants possessing this abnormality may be uniquely prone to central and cardiorespiratory depression resulting from hyperthermia, hypercarbia and hypoxemia during sleep. Death ensues due to failure of the arousal mechanism. This theory supports the notion of placing an infant in the supine (or non-prone) position during sleep, as prone positioning increases the likelihood of the nose and mouth becoming buried in the sleep surface.

Prior 1990, it was recognized that prone sleeping was one of several potential risk factors for SIDS (4). This association was strongly demonstrated in population based, case-control studies conducted in England, New Zealand and Australia. In 1992, the National Institute for Child Health and Human Development convened experts to deliberate on the potential relationship between prone sleeping and SIDS in the United States. Based on their opinion, the American Academy of Pediatrics (AAP) issued a recommendation that healthy newborns be placed on their side or back to sleep. In 1994 the "Back to Sleep" campaign was initiated to inform the public about the risks associated with prone sleeping. In the United States, the frequency of prone sleeping has declined from >70% to approximately 20% with a parallel decrease in the rate of SIDS by >40%. It has been demonstrated that non-prone positioning during sleep is beneficial to preterm/low birth weight infants as well as term infants (5). Current efforts are being made to target African Americans and other infant caregivers (sitters and daycare center personnel) with the "back to sleep" message as the incidence of SIDS still remains relatively high in these populations.

Another modifiable risk factor is the use of soft sleep surfaces and loose bedding (2). Polystyrene bead-filled pillows have been removed from the market. Pillows, quilts, comforters, sheepskins and porous mattresses pose additional risks particularly when placed under the infant. Although maternal smoking has been consistently identified in epidemiologic studies as a major risk factor for SIDS, changing behavior is difficult to accomplish. Bed sharing may pose an additional risk factor; the mechanisms of which include the presence of loose bedding, the possibility of the parent rolling onto the child, entrapment, and rolling of the infant to the prone position. The risk of SIDS associated with co-sleeping is significantly greater among smokers. No specific factors have been identified that are protective against SIDS.

There have been a number of other causes of infant death mistaken for SIDS, the most disturbing of which is infanticide (6). As the occurrence of cases of true SIDS decreases, the proportion of unexplained infant deaths attributable to fatal child abuse may be increasing. It is estimated that infanticide is the cause of 1% to 5% of cases identified as SIDS. In Great Britain, covert video surveillance revealed child abuse in 33 of 39 cases referred for evaluation of recurrent apparent life-threatening events (ALTEs). Intentional suffocation was observed in 30 patients. In addition, 12 out of 41 siblings of these patients had previously died suddenly and unexpectedly. Because autopsy findings cannot distinguish between deliberate asphyxiation and SIDS, certain circumstances should raise concern:

1. Previous recurrent cyanosis, apnea, or ALTE while in the care of the same person.
2. Age of death older than 6 months.
3. Previous unexpected or unexplained deaths of 1 or more siblings.
4. Simultaneous or nearly simultaneous death of twins.
5. Previous death of infants under the care of the same unrelated person.
6. Discovery of blood on the infant's nose or mouth in association with ALTEs.
7. Prolonged QT interval and short and medium chain acyl-CoA dehydrogenase deficiency (disorders of fatty acid oxidation) have also been identified in SIDS victims.

Managing the parents of the SIDS infant poses one of the greatest challenges to the health care provider. Most of these deaths occur at home. Parents are typically in shock, bewildered and very distressed. As in any infant death, guilt is often the prevailing response with the parent questioning what they could or should have done to prevent such a tragedy. Guilt is often compounded by anger and blame. The most appropriate professional response under these circumstances is to demonstrate compassion, empathy and support. It should be recognized that necessary medical questioning is likely to cause additional stress. Parental stress and feelings of guilt or paranoia have been further exacerbated by the professional and public awareness of infanticide as a contributing cause to sudden infant death. A SIDS training manual for emergency responders published by the Prince George's County, Maryland Police Department states the following "Do's" and "Don't's" which are equally relevant to the emergency department or primary care physician (7):

Do: Encourage the parent to be patient with him/herself and not expect too much.
Say you are sorry for what happened .
Allow the parents to express their grief as much as possible.
Reassure them that the child received the best care possible.

Don't: Tell the parents that you know how they feel.
Change the subject when the parent mentions their deceased infant.
Avoid mentioning the child's name.
Try to find something positive about the child's death.
Say the parent can always have another child.
Make comments that [previous] medical care may have been inadequate.

Parental anxiety and stress may be further heightened by naive and uninformed, yet well-intentioned family members. It is important to recognize that SIDS has a significant and life-long impact on parents and siblings, possibly leading to chronic emotional illness, divorce, or even suicide.

A recent AAP Policy Statement on SIDS, sleeping environment and sleep position states (2):

1. Infants should be placed for sleep in a nonprone position; supine preferred.
2. A crib that conforms to recognized safety standards is a desirable sleeping environment for infants.
3. Infants should not be put to sleep on waterbeds, sofas, soft mattresses, or other soft surfaces.
4. Avoid soft materials in the infant's sleeping environment.
5. Bed sharing or co-sleeping may be hazardous under certain conditions.
6. Overheating should be avoided.
7. Prone positioning is acceptable when the infant is awake and being observed so that issues related to development and positional plagiocephaly (head asymmetry and deformity) may be addressed.
8. Devices to maintain sleep position or to reduce the risk of rebreathing are not recommended.
9. Home monitors are available to detect cardiorespiratory arrest and may be of value for monitoring selected infants who have extreme cardiorespiratory instability. However, there is no evidence that such monitoring decreases the incidence of SIDS.
10. There is concern that the annual rate of SIDS appears to be leveling off as is the percentage of infants who sleep prone. Thus, the Back to Sleep campaign should continue and be expanded. Avoidance of maternal smoking, overheating, and certain forms of bed sharing should be included as important secondary messages.

In summary, although SIDS remains an enigma, it is reasonable to state that its etiology is multi-factorial and that an abnormal arousal response likely serves as the common denominator. The identification of a number of modifiable risk factors such as sleep position has effectively and dramatically reduced the incidence of SIDS through the application of prevention strategies. Other diagnoses, such as metabolic disorders, prolonged QT syndrome and infanticide account for a percentage of deaths mistaken for SIDS. Due to the unique nature of a SIDS death, sensitivity and compassion for parents and other caregivers is essential while thoroughly investigating the cause(s) of death.

Questions

1. True/False. Sudden Infant Death Syndrome has been nearly eradicated due to changes in infant positioning.

2. Which of the following disorders may mimic SIDS:
   a. galactosemia
   b. disorders of fatty acid oxidation
   c. maple syrup urine disease
   d. hypothyroidism

3. True/False. Co-sleeping is an acceptable practice if a mother is breast-feeding.

4. Infanticide should be considered in dealing with a SIDS death when:
   a. the parents are adolescents
   b. the infant is younger than 2 months of age
   c. previous ALTEs have occurred while under the care of the same person
   d. intrathoracic petechiae are present on post-mortem

5. True/False. Supine or non-prone positioning is beneficial in reducing the incidence of SIDS in infants born at <32 weeks gestation.

6. An appropriate response to a parent who has lost their child to SIDS is to:
   a. reassure them that they can always have another child
   b. use their infant's name often when speaking with them
   c. tell them you know how they feel
   d. speak critically about the previous medical management of their infant

7. True/False. Home cardiorespiratory monitors do not prevent SIDS.

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Answers to questions

1.False, 2.b, 3.False, 4.c, 5.True, 6.b, 7.True

Chapter IX.1. Infant Colic
Rodney B. Boychuk, MD

This is a 20 day old newborn that is brought to the emergency department at 10 pm with a chief complaint of extreme fussiness. His parents think he has abdominal pain as he is "gassy" and pulls his legs up as if he is trying to stool. He passes a lot of gas from his rectum and his parents can hear his stomach gurgling a lot. Tonight's episode has lasted for 4 hours with intractable crying, and his parents are very distraught. They have tried feeding, a pacifier, rocking, burping, changing the diaper, and inserting a rectal suppository but nothing has relieved the crying. He is currently feeding a standard cow's milk formula with iron without vomiting or diarrhea. Further questioning reveals this is the fourth day in a row that this has happened on a daily basis, usually in the evening, but the baby usually cries for about 2 to 3 hours.

He was born at term with no prenatal problems or infection at time of birth. No maternal use of illegal drugs. He has been feeding well with good weight gain and no fussiness until 4 days ago (age 16 days of age). No apnea, no vomiting, no fever, no constipation, no seizure activity, no trauma or history of shaking or abuse. He has been acting normally between daily episodes of fussiness.

Exam: VS T 37.0, P 130, RR 32, BP 80/55, oxygen saturation 100% in room air. Height, weight and head circumference are at the 50th percentile. He is a healthy appearing infant who is not crying at this time. He is alert and active. HEENT: Soft fontanelle, good eye contact. No evidence of corneal abrasion or watery eyes. Vigorously feeding during exam. No signs of closed head injury. Neck, heart and lung exams are normal. His abdomen is soft and non-distended. There is no definite tenderness. Bowel sounds are active. He has no inguinal hernias. His testes are normal. No tourniquets are noted over his penis and digits. He is moving all extremities well and his muscle tone is normal. He has no pain on movement. Color and perfusion good. No pallor or mottling of his skin is present.

Diagnostic impression by the physician: Unexplained recurrent crying with normal physical examination. Unclear etiology.

Colic is one of the most commonly made diagnoses during the first 4 months of life with a reported incidence of 10% to 35% of all infants. The word "colic" is derived from the Greek word "kolikos", which refers to the large intestine. Colic has also been called the three month colic, infant colic syndrome, or paroxysmal fussing in infants. The classic definition of infantile colic was described by Wessel (1) in 1954 as, crying lasting more than 3 hours per day, 3 days per week, and continuing more than 3 weeks in infants less than 3 months of age. During these paroxysms, the legs are often flexed, the infant may be described as gassy, and parents often think the infant has abdominal pain. In addition, crying is not relieved by normal parental interventions (feeding, burping, changing diapers, etc.).

How much crying is normal? In 1962, Brazelton (2) published characteristics of the median daily crying at various ages: At 2 weeks of age: 1 hour and 45 minutes. At 6 weeks of age: 2 hours and 45 minutes. At 12 weeks of age: less than 1 hour. The peak time for crying is 3:00 pm through 11:00 pm ("prime time"). Infants whose crying significantly exceeds these median values could be labeled as having "colic"; however, this is also dependent on the parents' ability to cope with crying and as to whether they label their infant's behavior as "normal crying" or "abnormal crying" (i.e., colic) (2).

The four clinical signs of colic are: 1) paroxysmal onset, 2) distinctive high-pitched pain cry, 3) physical signs of hypertonia and 4) inconsolability (3). Colic presents as intermittent and unexplained crying during the first three months of life by babies that are otherwise healthy. The "infant colic syndrome" (paroxysmal fussing) basically involves cyclic discrete periods of intractable crying, usually on a daily basis, with onset at 1-4 weeks of age (may be as early as the first week of age) and dramatic spontaneous improvement by 3-4 months of age. In addition to infant irritability, colic is characterized by recurrent episodes, excessive restlessness or activity, or diminished consolability. Colic is distinguished in that the crying is paroxysmal, intense and different in type from normal fussing and crying.

The defining elements of colic, according to Carey (4) are: full force crying for at least 3 hours per day, for 4 or more days per week, in infants who are less than 4 months old and are otherwise healthy. The infant begins a colic episode with a paroxysmal or sudden onset of crying. The cry reaches a screaming level, is often high pitched and coupled with facial grimacing indicating that the infant is in severe pain. There is increased motor activity, which may include flexion of the elbows, clenched fists, and generalized hypertonicity of the musculature, with the knees drawn up or legs stiff and extended. Milder cases of "colic" may exist, but defining this would be difficult.

There is no clear understanding of the etiology, pathophysiology and treatment of colic; however, proposed models for the etiology of colic fall into 3 broad categories: intrinsic or biological factors in the infant, extrinsic factors in the psychosocial environment and an interaction or systems approach.

The most important thing to remember about infants who present with intractable crying is this: ALL THAT CRIES IS NOT COLIC! Crying is a non-specific response in an infant, which may be a major symptom of an underlying pathologic process. The etiologies of intractable crying in infancy range from a benign phase of psychomotor development to a life threatening illness. The etiology is initially obscure and an accurate diagnosis is dependent on a knowledgeable and organized approach. A careful history and physical exam with selected laboratory studies usually establishes a diagnosis.

Since most of these patients initially present to the emergency department, the emphasis is on the evaluation of the infant or young child with intractable crying, and one must exclude serious underlying illness. In Poole's 1991 study (5) in afebrile infants, those who ceased crying before or during the initial assessment were unlikely to have a serious underlying illness, whereas the persistence of excessive crying after the initial examination was predictive of a serious underlying process. Therefore, do NOT discharge an infant or young child with persistent, excessive crying. Look for "red flags" in the history and physical, which suggest the possibility of significant underlying pathology (see Tables 1 and 2). The presence of any of these "red flags" should prompt a more extensive evaluation and aggressive management, often including specialty consultation and hospitalization (e.g., meningitis or sepsis).

Robert Bolte (6) has described "Red Flags" of non-colic causes of extreme fussiness, which may be signs or symptoms of life threatening illness, obtained by further history or physical examination. ANY OF THESE RED FLAGS SUGGEST NON-COLIC ETIOLOGIES OF FUSSINESS and must lead to extensive evaluation and aggressive management (Tables 1 and 2) (6). Do not make a diagnosis of colic on patients with any of these historical or physical examination "red flags" until other causes listed under "differential diagnosis" (Table 3) are ruled out.

Table 1 - Historical "Red Flags" Associated with Intractable Crying in Infancy (6)

1. Fever (>38 degrees C, 100.4 degrees F, rectal) in an infant less than twelve weeks of age.
2. Paradoxical irritability (infant doesn't want to be held).
3. Premature rupture of membranes (>24 hours), perinatal maternal fever/infection, neonatal jaundice.
4. Maternal drug use.
5. Poor feeding, poor weight gain.
6. Significant decrease in level of activity, cyanotic/apneic "spell", or seizure-like episode.
7. Bilious or projectile vomiting.
8. History not suggestive of classical "infant colic syndrome".
9. History suggestive of physical abuse (injury not consistent with reported history, inappropriate delay, non-maternal caretaker).
10. Antibiotic pre-treatment ("partially treated" sepsis/meningitis), particularly in the young infant.
11. History of recent head trauma.

Table 2 - Physical Examination "Red Flags" Associated with Intractable Crying in Infancy (6)

1. Fever (>38 degrees C, 100.4 degrees F, rectal) in the infant less than twelve weeks of age.
2. Hypothermia.
3. Heart rate >230.
4. Lethargy, poor eye contact.
5. Paradoxical irritability.
6. Pallor, mottling, poor perfusion, weak pulse.
7. Hypotonia, jitteriness, poor feeding.
8. Petechiae, ecchymoses.
9. Meningismus, full fontanel, head circumference >95%.
10. Retinal hemorrhages, signs of basilar fracture/closed head injury.
11. Tachypnea, retractions, nasal flaring, cyanosis.
12. Abnormal extremity movement (hip, etc.).
13. Abdominal tenderness/mass.
14. Bloody stool (not just external streaks).
15. Bilious or projectile vomiting.
16. Weight less than the fifth percentile for age.

Table 3 - Differential diagnosis of Infant Colic Syndrome(6):

I. Infectious
   1) otitis media
   2) meningitis/sepsis
   3) encephalitis
   4) urinary tract infection
   5) osteomyelitis, septic arthritis
   6) pneumonia
   7) gingivostomatitis, pharyngitis
   8) gastroenteritis
   9) Kawasaki Disease

II. Trauma
   1) child abuse - shaken baby
   2) corneal abrasion or foreign body in eye
   3) accidental fracture/musculoskeletal injury

III. Gastrointestinal/Genital
   1) intussusception
   2) reflux esophagitis (GERD)
   3) constipation/anal fissure
   4) midgut volvulus
   5) incarcerated inguinal hernia
   6) appendicitis
   7) milk protein intolerance
   8) testicular torsion
   9) penile tourniquet (from hair)

IV. Nutritional
   1) underfeeding

V. Respiratory
   1) hypoxemia/hypercapnia

VI. Metabolic
   1) hyponatremia, hypernatremia
   2) metabolic acidosis
   3) hypocalcemia/hypercalcemia, hypoglycemia, hyperglycemia
   4) inborn errors of metabolism

VII. Integument
1) diaper dermatitis
2) atopic eczema
3) burns (accidental and non-accidental)
4) foreign body (pin)
5) hair encirclement (strangulation of digit, penis, clitoris, uvula) diagnosed by a thorough physical exam
6) bites and stings

VIII. Drugs and Toxins
1) neonatal narcotic withdrawal
2) neonatal barbiturate, ethanol, hydantoin withdrawal
3) irritability related to smoking mothers who breastfeed
4) reaction to pertussis immunization
5) theophylline, antihistamine, decongestant, cyclic antidepressant, amphetamine, cocaine toxicity

A thorough history and a meticulous physical exam are the cornerstones of accurate diagnosis. Poole (5) described 56 afebrile infants who presented with unexplained excessive crying to the emergency department. The history provided clues to the final diagnosis in 20% of the cases, while the physical exam revealed the final diagnosis in 41% of the cases and provided clues to the final diagnosis in another 11%. Physical examination must start with a 2 or 3 minute period of observation from a distance with the child undressed, on the parent's lap. Assess the patient's appearance, distractibility, alertness, eye contact, ability to be comforted, respiratory rate and pattern, spontaneous extremity movement, etc. The extent of your work-up is usually determined from this observation period. Special emphasis should be given to the examination of the skin, palpation of the abdomen, eye examination (with funduscopic and eversion of the eyelids), evaluation of anterior fontanelle fullness, inspection of the tympanic membranes, oropharynx, and gums, palpation of extremities and clavicles, and performance of an anal rectal exam which may be done with a cotton tip swab.

If colic is determined to be the likely diagnosis, there have been a number of studies with varying results regarding treatment:

1. Taubman's (7,8) behavior-modification approach provides useful information for counseling parents (Table 4). His behavior-modification approach resulted in a 65-70% decrease of crying time (3.2 to 1.1 hours per day) in colicky infants in his 1984 and 1988 studies and a similar reduction in the crying time (3.8 to 1.1 hours per day) in a 1998 controlled study by Dihigo (9). This "good" approach assumes that colic results from inadvertent failure to respond to the infant's desires. The infant's crying is not a "cry of pain" but rather a way to communicate a need or desire. Taubman also described a "bad" approach (ignoring the baby) which assumes colic that results from over stimulation, therefore generally "ignoring" the baby (letting them cry) would be the logical treatment. The ignoring approach did not result in any decrease in the crying time in Taubman's 1984 study.

2. Simethicone (Mylicon, OTC) (10) (a non-toxic "defoaming" agent). The apparent effectiveness of simethicone (seen within 1-4 days in 54-67% of treated infants) probably represents a high-grade placebo effect. Simethicone converts gas foam into non-foam gas, but the gas remains in the bowel lumen.

3. Herbal tea (commercially available chamomile tea). Weizman, et al (11) showed that 57% of colicky babes improved (vs. 26% placebo), 5 oz. tea per dose with each colic episode not to exceed three times per day.

4. General counseling (6,7,12,13,14). Empathy and describing the natural history of colic to parents results in improvement by 3-4 months. Increased carrying time, automatic rocker swings, driving around the neighborhood (with baby in a car seat) and nap-time swaddling are benign measures that may be helpful.

Paregoric (tincture of opium), Bentyl (dicyclomine, possible association with SIDS) and Levsin (hyoscyamine sulfate, associated with anticholinergic toxicity) should NOT be used (6). Placing the infant in a car seat on the washing machine should NOT be used because of the possibility of falls and secondary head injury (6). Empiric formula changes are generally not useful, but this is a benign measure and it is often suggested. Mothers who are breast and bottle feeding should be encouraged to breast feed as much as possible and minimize formula feeding. Infants who are exclusively formula fed can be changed to a protein hydrolysate formula (Nutramigen, Pregestimil, Alimentum), as a trial to see if there is a beneficial response.

Table 4 - Good Colic Advice" for Parents: The underlying assumption of this advice is that continued crying in colicky infants results from the parents' inadvertent failure to respond to their infant's desires which the cries are signaling to the parents. The infant's crying is not a "cry of pain" but rather a way to communicate a need or desire.

1. Try to never let your baby cry.
2. In attempting to discover why your infant is crying consider these possibilities:
   a. The baby is hungry and wants to be fed.
   b. The baby wants to suck, although he/she is not hungry.
   c. The baby wants to be held.
   d. The baby is bored and wants stimulation.
   e. The baby is tired and wants to sleep.
   f. The baby needs his/her diaper changed.
3. If the crying continues for more than 5 minutes with one response, then try another.
4. Decide on your own in what order to explore the above possibilities.
5. Don't be too concerned about overfeeding your baby.
6. Don't be too concerned about spoiling your baby.

When infant crying continues despite all efforts to stop it, including feeding, do the following:

1. Put the baby in the crib and let him cry for up to one-half hour.
2. If still crying, pick the baby up for a minute or so to calm him/her then return him/her to the crib.
3. Repeat the above until the infant falls asleep or three hours have passed.
4. After three hours, feed the baby.
5. Do not shake the baby.

In summary, it is important to remember that crying is a non-specific response in an infant, which may be a major symptom of an underlying severe pathologic process and NOT necessarily just "colic." A careful history and examination combined with selected

laboratory studies usually establishes a diagnosis. Crying may simply be a normal response to stress such as hunger, discomfort, or over or under-stimulation, or may represent the "infant colic syndrome" (paradoxical fussiness). Close follow-up is crucial if the etiology of the irritability and excessive crying is still somewhat obscure at discharge. Do not discharge an irritable infant if "extreme fussiness" has not resolved, particularly if a "red flag" is present.

Questions

1. Which of these are NOT a feature of the infant colic syndrome?
    a. distinctive high-pitched pain cry
    b. inconsolability
    c. paroxysmal onset
    d. vomiting

2. Which of these is correct?
    a. colic usually occurs in infants greater than 3 months of age
    b. fever often accompanies colic
    c. colic is very rarely seen
    d. none of the above are correct

3. All of the following are correct regarding historical red flags, except:
    a. Red flags suggest that this intractable crying infant may not be due to the classic "infantile colic syndrome".
    b. Red flags include head trauma.
    c. Red flags exclude maternal illicit drug use.
    d. Red flags include paradoxical irritability.

4. Physical red flags include which of the following (check all that apply):
    a. fever
    b. lethargy
    c. poor feeding
    d. abdominal tenderness

5. True/False: Good advice for parents assumes their infant is trying to communicate a need or desire resulting from the parents inadvertent failure to respond to their infant's desires.

6. An acceptable approach(es) to infant colic include(s):
    a. Let the baby cry and ignore the baby.
    b. Put the baby in a car seat on the washing machine.
    c. Shake the baby to sleep.
    d. Try to discover why your infant is crying.

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Answers to questions
1.d, 2.d, 3.c, 4.abcd, 5.true, 6.d

Chapter IX.2. Abdominal Pain
Walton K.T. Shim, MD

This is a 6 year old female presenting with a 2 day history of crampy abdominal pain. The pain is located in the upper mid-abdomen and is associated with anorexia, nausea and four episodes of green vomitus. She appears to be weak and her parents noticed a decrease in urination. There is no history of diarrhea, trauma, fever or coughing. She has not passed any stools for the two days that she has been ill.

Her past history is significant for an appendectomy one year ago. Her family history is negative for other family members with similar problems.

Exam: VS T 37.0, P110, R 12, BP 100/60. She is alert and subdued. She moves without difficulty but cries episodically because of crampy pain. Her mucous membrane are sticky. Her eyes are sunken. Her neck is supple. Her heart and lungs are normal. She has a RLQ (McBurney's point) scar. She has moderate abdominal distention with hyperactive bowel sounds, peristaltic rushes and borborygmi with generalized mild tenderness. She has no inguinal hernias and her external genitalia are normal. A rectal exam finds no stool or mass. Her back is non-tender. Her skin turgor is decreased, but her overall color and perfusion are good.

CBC: WBC 14.0, Hgb 16, Hct 48, Na 132, K 3.0, Cl 90, bicarb 30. Urinalysis: SG 1.030, no pyuria or hematuria. Abdominal series radiographs show distended ladderlike small bowel with large air/fluid levels and no large bowel gas. No calcifications. Lung bases are normal.

Impression: Small bowel obstruction secondary to adhesions; dehydration, metabolic alkalosis and hypovolemia.

Abdominal pain is a common symptom of childhood. Its importance lies in differentiating the vast majority self-limited causes of pain from those few conditions that may be life threatening. In the latter category are those conditions that lead to a diagnosis of an "acute abdomen," usually leading to surgical intervention. Examples of these in children are most commonly acute appendicitis followed by incarcerated inguinal hernias, bowel obstruction, traumatic injury, ovarian torsion, pancreatitis, and biliary disease. Further complicating the diagnosis is the young child's relative inability to communicate and his/her inability to evaluate the abstract concept of pain.

In general, it is helpful to classify abdominal pain into two large categories: 1) pain originating in a hollow viscus, and 2) pain originating in a solid organ or the peritoneum.

Hollow viscus pain such as that of an the obstructed ureter, intestine, and gallbladder is colicky or spasmodic in nature. It coincides with the peristaltic waves of the organ as it attempts to overcome the distal obstruction such as ureteral or cystic duct stone or a fecal bolus in constipation. These waves or cramps are exactly what we experience with early acute appendicitis and gastroenteritis and are somewhat ameliorated by writhing and massage.

On the other hand peritoneal and solid organ pain such as caused by infection or trauma is aggravated by motion caused by coughing, abdominal compression, and walking. It is usually unrelenting or steady.

The search for the cause of abdominal pain is a good example of both inductive and deductive reasoning. In gathering data, a complete history and physical examination should suggest a disease process, a hypothesis or diagnosis (induction) which in turn should suggest a search for confirmative or corroborative data to strengthen or disprove the diagnostic hypothesis (deduction).

In evaluating the case above using inductive reasoning, the symptoms of crampy mid-abdominal pain, bilious vomiting, and history of prior abdominal surgery, suggest a hypotheses of bowel obstruction. If it is intestinal obstruction, an abdominal series should show an obstructive pattern (deduction).

It could be ureteral colic but this is uncommon in children and there is no blood in the urine indicating that a ureteral stone is unlikely. It could be biliary colic but this is rare in children and the pain distribution is not that of biliary pain. It could be a gynecological problem but this girl is prepubertal, and ovarian torsion frequently presents in the lower quadrant and radiates to the anterior thigh.

With a bowel obstruction, there may be bowel infarction. If there is gangrene by deduction there should be an elevated WBC, absent bowel sounds, marked tenderness, and localization of pain. Since none of these findings is present, bowel compromise (infarction) is unlikely.

The following data suggest dehydration by induction: urine specific gravity of 1.030, history of infrequent urination, sticky (dry) mucous membranes, sunken eyes and weakness.

In addition to peritoneal and hollow viscus pain, there is pain of neural origin. Nerve root compression by spinal cord tumors are rare but must be suspected if no other cause for the discomfort can be found and if the pain distribution is that of a dermatome. There should be no tenderness to palpation, but there may be hypesthesia.

Inflammation of the pleura from a pneumonic process in the distribution of the lower thoracic nerves is not an infrequent cause for referred abdominal pain and should be a reason for auscultation of the chest in a search for pneumonia or pleurisy. The abdominal series includes the lung bases and should be noticed when evaluating abdominal films. Lower lobe pneumonia can frequently be seen in the lung portions of an abdominal series, and it is very frequently overlooked since the clinician is usually focusing on the abdominal structures.

Diabetic acidosis, lupus erythematosus, porphyria, and other systemic illnesses may cause pain and inflammation of the serous surfaces (serositis). Some non-surgical causes of abdominal pain are lactose intolerance, inflammatory bowel disease, intussusception (sometimes requires surgery), Henoch-Schonlein purpura, ascariasis and acute gastroenteritis. Of help in the diagnosis of many of the non-surgical diseases is their chronicity or recurrence. Of course, the first occurrence of the symptoms is always more difficult to sort out.

Constipation is a common cause of chronic, recurrent and acute abdominal pain of varying degrees of severity. Relief after an enema is characteristic, but some cases are associated with more serious GI pathology, since the presence of constipation does not rule out the presence of something else, such as appendicitis.

As with most rules of thumb or generalizations there are exceptions that the clinician should keep in mind. One of these is that appendiceal pain always occurs in the right lower quadrant since the appendix is located there. However, since it is 6-13 cm long, its inflamed tip may come to rest anywhere in a radius of 6-13 cm from its base. This means that tenderness may be produced in the right upper quadrant, the midline, or in the suprapubic region. Similarly, if it is retrocecal so that it has no contact with peritoneum, the child may not exhibit severe tenderness. In its retrocecal position however, it may rest on the right psoas muscle and cause pain with active right hip flexion. If it lies on the right ureter, hematuria and pyuria may be produced.

Malrotation of the cecum may lead to all sorts of additional presentations for acute appendicitis. However, the astute clinician should keep in mind that rare things occur rarely and that when you hear hoof beats they are most likely horses and not gazelles or camels (in North America anyway).

The examiner of children must realize that most children wish to please, so that a child brought in the middle of the night to the hospital may feel obligated (obliged) to its adult caregivers and nighttime physicians to show cause for such concern. Thus, when asked if their tummy hurts, they may be inclined to answer affirmatively to justify the trip and trouble.

Similarly, older teenage boys with a macho image to uphold, may hesitate to admit pain and/or tenderness. It is a useful ploy to engage the child/teen in conversation about his or her dog, siblings or other familiar childhood topics while depressing the abdominal wall. Any true tenderness will be confirmed or refuted by involuntary guarding or its absence. A useful technique is to ask the child to cough while asking what he or she feels. This ploy will direct attention away from the abdomen but almost always elicits peritoneal discomfort if present.

Persistence and constancy of a sign heightens its importance in diagnosis. Tenderness should be reproducible. Sensory innervation of the intestines is via the ninth through eleventh thoracic nerve roots. Consequently pain from the intestines due to stretching is appreciated as originating from the mid-abdomen until an inflammatory process localizes it in the dermatome of the parietal peritoneum. There are several areas of referred pain which, when present, may suggest a specific entity. Radiation of flank pain into the groin and ipsilateral scrotum or labium suggests ureteral colic. Lower quadrant pain radiating to the anterior thigh should suggest torsion of the ipsilateral ovary and tube. A point of pain in either shoulder indicates subdiaphragmatic irritation from blood or pus. Right upper abdominal pain radiating around to the back suggests biliary tract involvement but epigastric pain radiating through to the back suggests a pancreatic origin.

The use of specific diagnostic tests should be guided by the clinical examination and evaluation. They should not be a substitute for such evaluation and should not precede the clinical examination since the clinical appraisal may obviate the need for additional tests. Plain film radiographs, ultrasound, computerized axial tomography (CAT scan), magnetic resonance imaging (MRI), and contrast studies may aid in the evaluation of abdominal pain but should be used judiciously. The flat and upright plain film radiographs can be particularly useful in recognizing small bowel obstruction, ileus, abnormal calcifications and lower lung pathology.

In summary, acute abdominal pain is a common childhood complaint. In most instances it usually passes without much interruption of the events of daily living. However, abdominal pain can also signal severe illness leading to serious morbidity and death if not attended to. Thus, separating the chaff from the wheat is extremely important. Persistence of pain associated with vomiting, dehydration and signs of inflammation should not be ignored, but should stimulate a thorough evaluation. The use of both inductive reasoning to formulate a hypothesis for the cause of the pain followed by deductive reasoning to confirm the hypothesis is the basis for identifying the correct diagnosis.

Questions

1. True/False: Surgical causes of abdominal pain are much less common than non-surgical causes.

2. True/False: Predicting a finding from a hypothesis is called deductive reasoning.

3. What characteristics differentiate hollow viscus from solid viscus and peritoneal pain?

4. Pain from distended intestines is appreciated in what area?

5. Where is the pain of urogenital origin referred?

Related x-rays

Challenging abdominal pain case: Yamamoto LG. Abdominal Pain with a Negative Abdominal Examination. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1994, volume 1, case 3. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v1c03.html

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Challenging abdominal pain case: Halm B. Right Lower Quadrant Pain in a 13-Year Old Female. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1996, volume 4, case 8. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v4c08.html

Abdominal pain with right sided calcifications: Yamamoto LG. Right-Sided Abdominal Pain in a 10-Year Old. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1996, volume 5, case 18. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v5c18.html

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Answers to questions

1. True
2. True
3. Crampy (hollow viscus) versus steady (solid viscus and peritoneal).
4. Mid-abdomen
5. Flank, groin and ipsilateral scrotum or labium

Chapter IX.3. Gastroenteritis and Dehydration
Sherloune Normil-Smith, MD

An 18 month old male is brought to the emergency department with a chief complaint of diarrhea and vomiting for 2 days. His mother describes stools as liquid and foul smelling, with no mucous, slime or blood. He reportedly is unable to keep anything down, vomiting after every feeding, even water. He has about 6 episodes of diarrhea and 4 episodes of vomiting per day. His mother reports that he is not feeding well and his activity level is decreased. He seems weak and tired. He has a decreased number of wet diapers. He attends daycare during the day when he is well. His last weight at his 15 month check up was 25 pounds (11.4 kg).

Exam: VS T 37.0, P 110, RR 25, BP 100/75, weight 11.3 kg (40th percentile). He is alert, in mother's arms, crying at times, and looks tired. HEENT: anterior fontanel closed, minimal tears, lips dry, mucous membranes tacky, no oral lesions or erythema, TMs normal. His neck is supple. Heart exam reveals mild tachycardia, no murmur. Lungs are clear. His abdomen is flat, soft, and non-tender with hyperactive bowel sounds. Testes are descended, non-swollen, non-tender. His diaper is dry. He moves all his extremities. No rashes are present. His capillary refill time is less than 3 seconds and his skin turgor is slightly diminished.

He is given 40 cc/kg of IV normal saline over two hours in the emergency department, but when given 30 cc of fluid to drink in the ED, he is unable to hold this down and he passes another large diarrheal stool. He is then hospitalized for further management.

Acute gastroenteritis is an ailment that is very common among children. During the first 3 years of life, a child will likely experience about 1 to 3 acute diarrheal illnesses. Diarrhea is defined as an increase in fluidity and volume of feces. Nearly all diarrheal infections are transmitted via the fecal-oral route. Many bacterial etiologies are also food borne.

When evaluating a child with diarrhea and/or vomiting, several important points and observations in the history and physical can help to assess severity and determine its etiology and pathogen involved. Information on the number, volume, and/or fluidity of stools and emesis should be obtained (1). However, this can be rather cumbersome if the number of episodes is large since recording the volume of each stool and emesis is unrealistic and not very helpful clinically, once the number of episodes exceeds 5 to 10. A history of fever, blood or mucus in the diarrhea, foul odor to the diarrhea, a large quantity of diarrhea or diarrhea for a prolonged duration are suggestive of a bacterial etiology. Diarrheal "mucus" is not something that is intuitive to most parents. The best question to ask is whether they have noticed any slimy, gooey, gelatinous, or mucous-like material in the diarrhea. The presence of mucus in the diarrhea is generally indicative of sheets of white blood cells in the diarrhea. The vomiting history should determine whether the vomitus is bilious or bloody (i.e., red or brown) and whether this is associated with abdominal pain. Parents will often convey that the vomitus contains mucus, but unlike the mucus in diarrhea, this is normal gastric mucus that is not helpful clinically. Other important historical items include: weight loss, dietary (intake) history, ill contacts and travel history. The physical exam should focus on signs of dehydration, conditions that may suggest an acute surgical condition and other systemic conditions which may cause these symptoms. The differential diagnosis of vomiting is extensive including systemic conditions such as meningitis, increased intracranial pressure, heart failure, pneumonia, urinary tract infection and many acute surgical conditions such as appendicitis, intussusception, midgut volvulus, etc. The differential diagnosis of diarrhea is more limited and is most often due to gastroenteritis.

Many organisms can cause acute infectious diarrhea and vomiting. These include bacteria, viruses, and parasites. Bacterial etiologies include: Campylobacter, E. coli, Staph aureus, Salmonella, Shigella, Vibrio, Yersinia and a few others. Viral gastroenteritis is by far more common. Amebic and parasitic etiologies are not very common in the United States, but such cases are treatable, making the identification of the pathogen essential.

Lab tests available include: CBC, stool Wright stain, stool culture, stool Rotazyme, serum electrolytes and glucose. In most instances, no laboratory studies are required. A CBC might raise the clinical suspicion of a bacterial etiology if a very high band count is present; however, this may also occur in viral etiologies, therefore it is not very helpful in most instances. A positive stool Wright stain identifies WBCs in the stool. This is suggestive of a bacterial etiology (similar to the history or observation of mucus in the stool), but since it is unable to determine the specific pathogen, it does not help clinicians in determining whether antibiotics are indicated. Thus, in most instances of gastroenteritis, a Wright stain is not helpful. A stool culture can be obtained by swabbing a diarrhea sample or by inserting a swab into the rectum, then rotating it to obtain organisms from the rectal mucosal surface. This latter method is called a rectal swab and it has a higher yield for identifying enteric pathogens, which are more likely to be found on the rectal mucosal surface than in the diarrhea itself. Thus, if a stool culture is to be obtained, it should be done via a rectal swab. A stool Rotazyme is a rapid test which identifies the presence of rotavirus in the diarrhea. A positive Rotazyme negates the need for a stool culture and antibiotic therapy. Serum electrolytes and glucose may be helpful in determining the degree of electrolyte imbalance, metabolic acidosis and hypoglycemia.

Campylobacter

Campylobacter is a major cause of diarrhea in the world. Many species have been identified as enteropathogens, but C. jejuni and C. coli are the two predominant species causing acute diarrhea in humans. C. jejuni is the most commonly documented bacterial cause of diarrhea. Transmission occurs by the fecal-oral route, through contaminated food and water or by direct contact from infected animals and people. The main source of C. jejuni and C. coli infection in humans is poultry, although dogs, cats, and hamsters are also potential sources. Outbreaks of diarrhea caused by C. jejuni and C. coli have been associated with consumption of undercooked poultry, red meat, unpasteurized milk and contaminated water. In industrialized nations, C. jejuni mainly affects children younger than 5 years of age, and individuals 15-29 years old. In temperate climates, infections occur mostly during the warm months, and in tropical climates, the incidence is greater during the rainy season. Prodromal symptoms begin after an incubation period of 1-7 days. These include fever, headache, chills and myalgia. Diarrhea accompanied by nausea, vomiting, and crampy abdominal pain occurs within 24 hours. Stools vary from loose and watery, to grossly bloody. Abdominal pain affects more than 90% of patients older than 2 years, and if severe enough, may mimic appendicitis. The clinical presentation may also mimic inflammatory bowel disease. Gradual resolution is to be expected, but in 20% of cases, diarrhea can last longer than 2 weeks. The variation in clinical presentation of Campylobacter diarrhea makes clinical diagnosis difficult. In order to differentiate it from other causes of colitis such as Salmonella, Shigella, E. coli 0157:H7, one has to rely on microbial diagnosis (2).

Rehydration and correction of electrolyte abnormalities are the mainstay of treatment. The use of antimicrobial therapy remains a controversial issue since resolution without antibiotics usually occurs, but early initiation of antibiotic therapy can shorten the duration of infectivity (i.e., the excretion of the organisms), and the duration of symptoms. Erythromycin is the antibiotic of choice for the treatment of C. jejuni enteritis. Since it is not possible to reliably identify Campylobacter as the etiology prior to a positive culture, erythromycin is

generally not prescribed until several days after a culture has been obtained. A notable exception might be when diarrhea develops in a contact of an individual who was known to have Campylobacter gastroenteritis.

C. jejuni has also been associated with septicemia, abortion and Guillain-Barre syndrome. C. pylori, now called Helicobacter pylori, does not cause diarrhea, but is associated with peptic ulcer disease. C. fetus rarely causes diarrhea, but is recognized as a cause of fever, bacteremia in immunocompromised hosts, and spontaneous abortion.

Escherichia coli

E. coli is one of the most common causes of bacterial diarrhea in humans worldwide. Normal bowel flora consists mostly of E. coli; however, some strains of E. coli are pathogenic. Several categories of E. coli cause diarrhea: EHEC (enterohemorrhagic), ETEC (enterotoxigenic), EIEC (enteroinvasive), EPEC (enteropathogenic), and EAEC (enteroaggregative).

EHEC causes a hemorrhagic colitis syndrome manifested by bloody diarrhea without fever. Illness is characterized by abdominal pain with diarrhea that is initially watery, but becomes blood streaked or grossly bloody. E. coli O157:H7 has most commonly been associated with this syndrome, which can also be caused by other strains of EHEC which produce large quantities of a potent cytotoxin. The cytotoxin produced by E. coli is called Verotoxin 1, and is virtually identical to the shigatoxin. Unlike shigellosis or EIEC disease, fever is uncommon in this diarrheal illness. The strains of E. coli producing this potent cytotoxin, are important because 5% to 8% of symptomatic patients go on to develop hemolytic uremic syndrome (HUS).

ETEC typically causes explosive diarrhea, accompanied by nausea, vomiting, abdominal pain, with little or no fever. Symptoms resolve in a matter of days, but these organisms can have a major effect on the hydration status of infants. ETEC is often responsible for the syndrome of "traveler's" diarrhea, since it is more common in non-industrialized countries (note the "T" in enteroToxigenic and Traveler's).

EIEC causes a dysentery-like illness or watery diarrhea caused by an enterotoxin called the EIEC enterotoxin. This illness is clinically indistinguishable from shigella dysentery, and is characterized by fever, abdominal pain, tenesmus, watery or bloody diarrhea.

EPEC rarely causes diarrhea in older children and adults, but has been incriminated in sporadic and epidemic diarrhea in infants and children in the first 2 years of life. This can be remembered as pediatric diarrhea (note the "P" in enteroPathogenic and Pediatric). The diarrhea is non-bloody, and contains mucus. These organisms can cause prolonged diarrhea, especially in the first year of life, a feature that in not shared by the ETEC, EIEC, or EHEC.

EAEC have been associated with acute and chronic diarrhea in developing countries. They can cause significant fluid losses. Like EPEC, these organisms can cause a prolonged diarrhea, and severe abdominal pain, lasting 2-4 weeks.

Management of fluid and electrolyte losses should be the focus of treatment. Early refeeding (within 8-12 hours or initiation of rehydration) should be encouraged, because a prolonged delay in feeding can lead to chronic diarrhea and dehydration. The decision to treat with antibiotics is difficult, because of the lack of a rapid diagnostic test. EPEC and ETEC respond well to treatment with trimethoprim-sulfamethoxazole, but antimicrobial treatment of EHEC organisms may increase the risk of hemolytic uremic syndrome (1). Thus, it is preferable to withhold antibiotics until a culture proven etiologic indication for antibiotics is determined.

Staphylococcus aureus

S. aureus is a major cause of food poisoning. Symptoms begin within 1-6 hours after ingestion contaminated with preformed S. aureus heat-stable enterotoxins. Symptoms include nausea, vomiting, abdominal pain, diarrhea without fever, and last less than 12 hours (1).

The term "food poisoning" describes a phenomenon in which bacterial contamination of food results in toxin production by the bacteria. This toxin ingestion is what causes the acute symptoms. Typically, the onset after exposure is rapid (i.e., no incubation period is required) and resolution is relatively rapid. Food poisoning should be distinguished from food borne infection, in which the latter is due to contamination of food which is ingested and symptoms develop several days later after a period of incubation.

Salmonella

Salmonella is one of the most frequently reported causes of food borne outbreaks in the United States. Three main species are identified: S. cholerae-suis, S. typhi (known as typhoid), and S. enteritidis. Salmonella gastroenteritis occurs throughout life, but is most common in the first year of life. Many outbreaks of S. enteritidis have been associated with ingestion of contaminated eggs. For clinical disease to occur, 10,000 to 100,000 viable organisms must be ingested. The incubation period for salmonella gastroenteritis is 6 to 72 hours. The major virulence trait of salmonella species, especially S. typhi, is their ability to invade the intestinal epithelium. Nontyphoidal salmonella can also display this trait, but most are associated with watery diarrhea. Salmonella causes several clinical syndromes: 1) acute gastroenteritis, 2) a subacute or prolonged carrier state, 3) enteric fever, bacteremia or both, and 4) dissemination with localized suppuration (i.e., abscesses), osteomyelitis, or meningitis (3).

The most common manifestation of disease caused by salmonella is gastroenteritis. The most prominent symptom is diarrhea, which is usually self-limited, lasting 3-7 days. However, the diarrhea can range from a few stools, to profuse bloody diarrhea to a cholera-like syndrome. Abdominal cramps and fever are usually present (3).

The diagnosis is made by stool culture. Antimicrobial agents such as ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole and some third generation cephalosporins can be used in patients with severe and progressing disease. Initiation of empiric antibiotic treatment is not indicated unless: 1) the infant is very young, 2) the patient is immunocompromised, or 3) sepsis or disseminated infection is suspected.

Shigella

Infection by shigella is rare in the first 6 months of life, but is common between 6 months and 10 years, and is most common in the 2nd and 3rd year of life. There are 4 major serogroups of Shigella: S. sonnei, S. flexneri, S. boydii, and S. dysenteriae. S. sonnei and S. flexneri are more common causes of diarrhea in the U.S. and Europe. Infection occurs mostly during the warm months in temperate climates, and during the rainy season in tropical climates. Transmission is mainly via person-to-person contact and by contamination of food and water. Only a small inoculum of shigella is required to cause illness (as few as 10 organisms). After ingestion, an incubation period of 12 hours to several days follows, before the development of symptoms. Shigella organisms invade the epithelial cells of the colon, causing colitis. Infected individuals may present with: 1) asymptomatic excretion, 2) enterotoxin-like diarrhea, 3) bacillary dysentery (bloody diarrhea), 4) arthritis similar to Reiter's, 5) HUS after infection with S. dysenteriae (1).

Diarrhea is initially watery and of large volume, and develops into frequent small volume, bloody and mucoid stools. Other clinical features include, vomiting, severe abdominal pain, high fever, and painful defecation. As many as 40% of children with bacillary dysentery will develop neurologic findings. Seizures, headache, confusion, lethargy, and/or nuchal rigidity may be present before or after the onset of diarrhea. In very young and malnourished patients, sepsis and disseminated intravascular coagulation can develop as complications. When sepsis occurs, the mortality rate is high. In those infected with S. dysenteriae serotype 1, hemolytic anemia and hemolytic uremic syndrome are common complications caused by shigatoxin. Post infectious arthritis occurs 2 to 5 weeks after dysenteric illness, and is seen characteristically in patients with HLA-B27 (1).

Stool culture (rectal swab) is the gold standard for diagnosis. The presence of fecal leukocytes, fecal blood, and a CBC leukocytosis with left shift can help support a presumptive diagnosis of bacterial gastroenteritis. Fluid and electrolyte correction and maintenance should be the initial focus of treatment. Drugs that delay intestinal motility (Lomotil, loperamide) should be avoided. Empiric antibiotic treatment of all children strongly suspected of having shigellosis is highly encouraged, and should be initiated as soon as possible. However, other bacterial etiologies may be worsened by antibiotic treatment, so it may be preferable to await culture results.

Vibrio cholera and parahaemolyticus

Vibrio species are common causes of diarrhea worldwide. V. cholera serogroups O1 and O139 have been responsible for cholera epidemics in many developing countries. These serogroups produce profuse watery diarrhea (known as rice water stools) after adhering to and multiplying on small intestinal mucosa. They cause diarrhea by producing several toxins. The most important toxin is the cholera toxin which is a heat stable enterotoxin. V. parahaemolyticus is a common marine organism found in water, shellfish, fish, and plankton. It is generally an uncommon cause of diarrhea, but people who consume raw shellfish and seafood are at higher risk. Infected individuals experience diarrhea, abdominal cramps, nausea, and less frequently, vomiting, headache, low grade fever and chills (1).

Yersinia enterolitica

Y. enterolitica is a gram negative bacillus that appears to be a common cause of gastroenteritis among children in Europe and Canada, but is uncommon in the United States. Outbreaks have been associated with ingestion of contaminated milk or food. The clinical manifestations vary depending on the age of the involved person. It usually causes acute gastroenteritis in younger children, and mesenteric adenitis in older children. Most infections occur in children 5 to 15 years of age, and incidence is greater during the winter months. Children younger than 5 years old usually have self-limited gastroenteritis, lasting from 2 to 3 weeks. Symptoms include diarrhea accompanied by fever, vomiting, and abdominal pain. The abdominal pain is colicky, diffuse, or localized to the right lower abdomen. Stools may be watery, containing blood or mucus, and fecal leukocytes are commonly present. Children older than 6 years often present with abdominal pain associated with mesenteric adenitis that mimics acute appendicitis. Intussusception secondary to Y. enterolitica has also been described in children.

While isolation of Y. enterolitica from stool specimens is difficult, it is readily isolated from blood or lymph nodes. Serologic diagnosis can be obtained with enzyme-linked immunosorbent assays. Antibodies are detectable from 8-10 days after the onset of clinical symptoms, which persist for several months.

Y. enterolitica gastroenteritis is usually self-limited, therefore antibiotic therapy is only indicated for complicated infections, and compromised patients. It is usually susceptible to trimethoprim-sulfamethoxazole, aminoglycosides, tetracycline, chloramphenicol, and third generation cephalosporins. It is resistant to penicillin, ampicillin, carbenicillin, erythromycin, and clindamycin (4).

Other bacteria

Other bacteria that cause an acute diarrheal illness include Bacillus cereus, Aeromonas hydrophila and Plesiomonas shigelloides. Clostridium difficile is associated with pseudomembranous colitis, and Clostridium perfringens can cause a short duration food poisoning syndrome.

Viral gastroenteritis

Diarrhea and vomiting caused by viruses are usually self-limited. It usually manifests as watery diarrhea, without blood or mucus. The most common accompanying symptom is vomiting. Other symptoms include abdominal cramps, nausea, headaches, myalgias and fever. Four viral groups are regarded as medically important causes of acute gastroenteritis (rotaviruses, astroviruses, enteric adenoviruses, and calciviruses). They are all spread largely via the fecal-oral route.

Rotavirus accounts for 82,000 hospitalizations and 150 deaths per year in the United States. It is a very common cause of acute gastroenteritis in infants and children, responsible for over 50% of cases of acute diarrhea in children. Rotavirus causes severe illness in children 6-24 months. Most children (more than 90%) have been exposed to rotavirus by their 3rd birthday. It is the most common cause of diarrhea in infants and children in the winter months in colder climates, and is responsible for 35-50% of hospitalization for infants and children with acute diarrhea. Clinical features range from asymptomatic infection, to diarrhea preceded by severe vomiting. The incubation period is 2-4 days, and viral shedding occurs from a few days before, to 10 days after the onset of illness. Newborns tend to have asymptomatic infections in the first few months of life, because transplacental antibodies and breastfeeding are protective. Clinical symptoms in infants and children usually consist of fever, abrupt onset of vomiting and watery diarrhea. One third of children will also have a concurrent respiratory infection. The diagnosis can be made by a number of enzyme immunoassays (Rotazyme) and latex agglutination tests with good specificity and sensitivity. Stools collected early in the course of the illness are more likely to contain virus, than those collected 8 or more days after the onset of illness. Treatment is directed toward correction of dehydration with oral fluid replacement. Breastfeeding is the most important and available preventive strategy, because human colostrum contains rotavirus antibodies (5).

Adenovirus commonly causes a wide range of human diseases, including conjunctivitis, pneumonia, and upper respiratory infections. A subgroup of adenovirus (enteric adenovirus) has been found to cause acute gastroenteritis, lasting 4 to 20 days. After rotavirus, enteric adenovirus is the next most common cause of viral gastroenteritis in infants and children, accounting for 5% to10% of hospitalizations for acute gastroenteritis in children. They have been linked to outbreaks in child care centers, and asymptomatic excretion can occur. Most episodes occur in children less than 2 years. Infection increases in the summer months. Symptoms are indistinguishable from those associated with rotavirus but are less severe. The diagnosis is a presumptive one. Research laboratory confirmation can be made by solid phase immunoassays, electron microscopy, and viral culture but these studies are not routinely available. As with rotavirus, treatment is aimed at replacing fluid losses, and at correcting electrolyte abnormalities (5).

Caliciviridae primarily infect infants and young children. Human caliciviruses (HuCVs) have been associated with outbreaks from contaminated food or water in restaurants, schools, hospitals, summer camps and cruise ships. They are divided into 4 genera: Norwalk-like calciviruses (which causes illness mostly in adults), Sapporo-like calcivirus (which primarily cause pediatric gastroenteritis), rabbit-like calcivirus, and swine-like calicivirus. Hepatitis E, which was previously classified as a calcivirus, is no longer classified in this family. The gastroenteritis is indistinguishable from that of rotavirus. The incubation period is 12 hours to 4 days. Excretion lasts 5-7 after the onset of symptoms, and can continue for 4 days after the resolution of symptoms (5). The diagnosis is presumptive, but epidemiologic and research confirmation of these etiologic agents can be made by electron microscopy.

Astrovirus infection is believed to occur very commonly, since 80% or more adults have antibodies against the virus. They cause watery diarrhea, especially in children younger than 4 years. Symptoms are mild, consisting of fever and malaise, followed by watery diarrhea. Vomiting is uncommon. The incubation period is 3 to 4 days, and excretion typically lasts for 5 days after onset of symptoms (5).

Protozoan and parasitic gastroenteritis

Several protozoans cause diarrhea: Giardia lamblia, Entamoeba histolytica, Cryptosporidium parvum, Isospora belli, Microsporidium species, and Cyclospora cayetanensis. Within the intestinal tract, 3 organisms, namely Giardia lamblia, Entamoeba histolytica, and Cryptosporidium parvum are the most important.

Infection with E. histolytica occurs more frequently in tropical countries, especially in areas with poor sanitation. The life cycle of E. histolytica has 2 stages: the trophozoite which is found in diarrheal stools, and the cyst, which is more predominant in formed stools. The cysts are transmitted primarily by the fecal-oral route in contaminated food and water. The minimum incubation period is 8 days, but ranges up to 95 days. The clinical symptoms that occur in patients with amebiasis consist of: 1) Intestinal amebiasis, with the gradual onset of colicky abdominal pain and frequent bowel movements, tenesmus, and flatulence. 2) Amebic dysentery, characterized by profuse diarrhea containing blood, mucus, and constitutional signs such as fever and dehydration. 3) Hepatic amebiasis, presenting with an amebic abscess within the liver often without diarrhea. 4) Asymptomatic infection. E. histolytica can usually be identified in stool samples, or acute infection can be confirmed by serology. Metronidazole is the treatment of choice.

Giardia lamblia is a flagellated protozoan that is a major cause of diarrhea, especially in patients who travel to endemic areas. It is the most common intestinal protozoan found in the United States. Children seem to be more susceptible to Giardia than adults. Like E. histolytica, the life cycle consists of 2 stages: the trophozoite (motile form), and the cyst. IgA deficiency and hypogammaglobulinemia predispose patients to symptomatic infection. The clinical manifestations are foul-smelling diarrhea, with nausea, anorexia, abdominal cramps, bloating, belching, flatulence, and weight loss. Abdominal distention and cramps can last for weeks to months. The illness is usually self-limited, lasting 2 to 6 weeks, but may become chronic. Chronic symptoms can include fatigue, nervousness, weight loss, steatorrhea, lactose intolerance, and growth retardation. The easiest way to diagnose Giardia is by identifying cysts in a stool specimen. However, these specimens are frequently falsely negative. The diagnosis can also be made by antigen detection tests, endoscopic examination of the upper small intestine, by mucosal biopsy or by collection of jejunal contents. The treatment of choice for both symptomatic and asymptomatic patients is furazolidone or metronidazole. An alternative drug is quinacrine (6).

Cryptosporidium organisms are small protozoans that are a common cause of enteric infection worldwide. The oocyst form of cryptosporidium is found in feces, and is the infective form. Cryptosporidium parvum is thought to be the cause of infection in humans. Cryptosporidium causes cryptosporidiosis mainly in immunocompromised patients, infecting approximately 3% to 4% of patients with AIDS in the United States. Another high risk group for acquiring infection with this organism, are children 6 to 24 months old. It is acquired by fecal-oral transmission, and has an incubation period of 2 to 14 days. Because the oocyst is highly stable in the environment, contaminated drinking water, swimming pools and apple cider are major sources of outbreaks. Several outbreaks of diarrhea in day care centers have been attributed to cryptosporidium. In the United States, 13% of children less than 5 years old, 38% of those 5 to 13 years of age, and 58% of adolescents 14 to 21 years old are seropositive for C. parvum. Symptoms are self-limited in immunocompetent patients, consisting of watery nonbloody diarrhea, accompanied by vomiting, flatulence, abdominal pain, myalgias, anorexia, weight loss, and low-grade fever. Symptoms last an average of 9 days in immunocompetent patients, but can last months in immunocompromised hosts, causing large fluid losses, profound malabsorption and weight loss. The diagnosis of cryptosporidiosis is made by demonstrating the presence of cryptosporidium oocysts in stool specimens. Patients with diarrhea who attend day care centers, those with AIDS or other immunodeficiencies are at higher risk. There is no specific antimicrobial therapy for cryptosporidiosis (7).

Dehydration

Fluid losses resulting from acute vomiting and diarrhea can lead to dehydration. Diarrhea is the most common cause of dehydration in infants and children, and is a leading cause of death worldwide in children less than 4 years of age. Quantifying the degree of fluid loss by history and the amount and type of fluid intake can help to determine dehydration severity and the risk of electrolyte imbalance. The amount of urine output and the presence or absence of tears as well as the presence of documented weight loss, can help determine the severity of dehydration present. Other important aspects of the history include the presence of fever, sweating and hyperventilation, which may cause insensible losses, contributing to the degree of dehydration.

The vital signs can offer clues on the degree of dehydration present. Tachycardia can indicate moderate dehydration, whereas hypotension is a late sign of severe dehydration. The absence of tachycardia cannot be used to rule out dehydration. An increase in the respiratory rate is associated with a higher degree of dehydration, whereas in mild dehydration, the respiratory rate is normal. Attention should be paid to the child's overall appearance and mental status (alert, irritable, tired-appearing, poorly responsive, unresponsive). Other pertinent exam findings include the fontanelle (sunken or not), the eyes (presence or absence of tears, sunken or not), the mouth (dry lips, tacky or sticky mucous membranes), the skin (cool or warm, skin turgor). Measurement of the capillary refill time is a variable and unreliable indicator of dehydration. It should be performed in a warm room. Light pressure is applied to the finger nailbed. And the time from blanching to restoration of color to the nailbed is measured. It may be preferable to assess capillary refill centrally (over the chest or forehead) and peripherally (fingers), so that the two can be compared. A delay of less than 2 seconds is normal. Delays of 2 to 3 seconds may indicate moderate dehydration, and more than 3 seconds in delay may indicate severe dehydration. Most children with clinically significant dehydration, will have 2 of the following 4 clinical findings: 1) capillary refill greater than 2 seconds, 2) tacky mucous membranes, 3) no tears, and 4) ill appearance (8).

Management

The decision to hospitalize or to attempt outpatient management will be based on the clinical findings, combined with a history of fluid intake, the frequency of urination, assessment of concurrent stool losses and the response to therapy.

Once a child is presumed to be dehydrated, the degree of dehydration needs to be determined. Acute weight loss can be used to determine the degree of dehydration, but accurate baseline weights in growing children are almost never known. Clinical criteria can be used to estimate degrees of dehydration. Mild dehydration is 5% or less, moderate is about 10%, and severe dehydration is about 15% or greater. This classification is relative and not well standardized. If severe dehydration or uncompensated shock is present, the patient should be immediately treated with an IV fluid infusion (20 cc/kg of normal saline or lactated Ringer's) to restore the intravascular volume. It is likely that more than one fluid bolus may be necessary to restore the patient's intravascular volume, since 20 cc/kg only corrects 2% of the body weight. Therefore, the patient should be reassessed after each fluid bolus (8).

Children with mild to moderate dehydration can be initially treated with oral rehydration. Contraindications to oral rehydration therapy (ORT) include severe dehydration, intractable vomiting, and severe gastric distention. Children who had initially received IV fluid infusions for severe dehydration who now feel well enough to take oral fluids should also be considered for oral rehydration. Oral rehydration therapy (ORT) can be as effective as IV therapy. It is noninvasive and inexpensive. The AAP recommends that rehydration solutions contain 70-90 mEq/L of sodium, 20 mEq/L of potassium, and 2.0-2.5 grams/dL glucose. Examples of rehydration solutions (ORS) are: Rehydralyte (70mEq/L Na, 20 mEq/L K, 2.5% glucose, and the WHO solution (90m Eq/L Na, 20 mEq/L K, 2% glucose). ORT should initially be given in small, frequent volumes, 5 to 20 cc every 5-10 minutes, and advanced slowly to approach 5 cc/min. The degree of dehydration and the presence of ongoing losses dictate the volume of fluids to be administered. If the degree of dehydration is mild (3-5%), the volume of ORS administered should be 50 cc/kg (i.e., 5% of the body weight) over 4 hrs. Those with significant dehydration (5-10%) should received 100 cc/kg (i.e., 10% of the body weight) of ORS over 4 hours. In either case, an additional 10 cc/kg should be given for each diarrheal stool seen. Once rehydration is complete, maintenance fluid is given. Examples of maintenance oral solutions are: Pedialyte and Infalyte, containing 45-50 mEq/L Na, 2-2.5 mEq/L K, 1.5-2.5% glucose (9).

Patients with mild dehydration can potentially be managed without laboratory analysis. However, in moderate or severe dehydration, laboratory studies should be obtained to look for electrolyte abnormalities of to measure the degree of metabolic acidosis.

Children who are severely dehydrated and those who cannot retain oral fluids because of intractable vomiting should be hospitalized and treated with IV fluid. Once the initial resuscitation phase is completed, replacement IV therapy should be instituted, taking into account fluid and electrolyte deficits as well as ongoing losses. Usually, half of the replacement therapy in addition to the maintenance fluid requirement is given over the first 8 hours, and the second half is given over the next 16 hours. However, patients with hypernatremic dehydration (serum sodium >150mEq/L) require special intervention. After initial management with normal saline or lactated Ringer's, the replacement fluid is given more slowly, over 48 hours or more. This is done because rapid correction of hypernatremia can result in acute brain swelling, brain herniation, and death. Therefore, care should be taken to avoid dropping the serum sodium by more than 15mEq/L per 24 hours.

Once a child is adequately rehydrated, the question of when to start feedings arises. It was previously perceived that a period of "gut rest" should follow rehydration of patients with acute gastroenteritis. However, numerous trials have shown no advantage to this strategy. The concept of early refeeding is replacing the old concept of "gut rest". Numerous trials have shown that early feeding of age-appropriate foods results in faster recovery. Breast fed infants should continue nursing despite diarrhea. Following rehydration, children with mild diarrhea who drink milk or formula can tolerate full strength feedings. The traditional BRAT diet (bananas, rice, applesauce, toast), although acceptable, should be considered to be a concept representative of a bland diet rather than a specific diet. Controlled clinical trials have shown that starches, complex carbohydrates (rice, wheat, bread, potatoes, cereals), soups, fresh fruits and vegetables, yogurt, and lean meats are better choices, and well tolerated (9). Fatty foods, juices, teas, sweetened cereals, soft drinks, are poor choices, and should be avoided. Some patients may benefit from lactose-free or low-lactose formulas.

Most pediatricians and experts recommend against using anti-diarrheal agents such as Imodium (loperamide), Pepto-Bismol (bismuth subsalicylate), and Kaopectate. This is more of a precaution since many studies do show some beneficial effects from these medications in patients with mild diarrhea. However, patients with mild diarrhea will get better on their own so these medications are usually not necessary. For young children with severe gastroenteritis, there is insufficient data to confirm the benefit and safety of these medications, which is why they cannot be recommended routinely at this time.

Questions

1. Which diarrhea causing organism may be also cause neurologic symptoms?
2. What is the most common viral cause of acute gastroenteritis, and what are its associated symptoms?
3. How is Giardia lamblia most easily diagnosed and how is it treated?
4. List 4 physical signs of dehydration in children?
5. How are children with mild dehydration initially treated?
6. How are children with severe dehydration initially treated?

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Answers to questions

1. Shigella.
2. Rotavirus. It causes fever, vomiting, and watery diarrhea.
3. The diagnosis can be made by antigen detection, identifying cysts in the stool, endoscopy or examination of jejunal contents. It is treated with metronidazole or furazolidone.
4. Sunken fontanelle, absence of tears, sunken eyes, sticky/tacky oral mucosa, delayed capillary refill, reduced skin turgor, inactivity/lethargy, tachycardia, hypotension.
5. With oral rehydration, small frequent volumes 5-20cc every 5-10 minutes, advanced slowly.
6. With IV fluid infusion of normal saline or lactated Ringer's at 20cc/kg. Oral rehydration with ORS is commonly employed in other countries.

Chapter IX.4. Biliary Atresia
Jason T. Nomura, MD

This is a 4 week old female who presents to the office with parental reports of increasing jaundice over the last week. Her parents report that 2 weeks ago, she began to have yellowing of her eyes with subsequent yellowing of her skin when she was diagnosed with physiologic jaundice. After persistent jaundice for 5 days, her parents changed her from breast-feeding to a commercial formula. Since the jaundice appears to be worsening, her parents decided to bring her in for re-evaluation. Her stools have been pale in color for the past 10 days along with darker urine.

She was born by spontaneous vaginal delivery to a G2P1 A+ mother at 39 weeks with Apgar scores of 9 and 9 and 1 and 5 minutes. There were no complications noted at birth, the nursery, or at discharge home. The patient was not jaundiced at discharge or when seen at initial office visits. Her highest bilirubin previously was 12.0 and her blood type is A+.

Exam: VS Normal. Weight and height are at the 60th percentile. She is awake, alert, in no acute distress and is easily comforted by her mother during the exam. Her skin is jaundiced, most notably in the cephalic and truncal areas, with scleral icterus. Her liver is slightly enlarged without nodularity. No splenomegaly is noted. The remainder of her exam is normal.

Laboratory examinations reveal a total bilirubin of 15 mg/dL, direct bilirubin of 12.3 mg/dL, ALT 45 U/L, AST 52 U/L, and an alkaline phosphatase of 2007 U/L. The patient undergoes a DISIDA scan after 5 days of phenobarbital therapy. The scan showed normal uptake by the liver but no excretion of the isotope (i.e., no bile flow) into the bowel even after 24 hours. She is referred to the surgical service for evaluation. She is then scheduled for a laparotomy with intraoperative cholangiogram, wedge liver biopsy and possible Kasai procedure.

Biliary atresia (BA) is a serious cause of infantile cholestasis and the most common cause of orthotopic liver transplantation in children. BA was originally thought of as the progressive fibrosis and obliteration of the extrahepatic biliary system. However, it is now known that the intrahepatic bile ducts are also affected by the disease process (1,2). The incidence of BA is not well known with individual studies reporting an incidence ranging from 1 in 8,000 live births to 1 in 25,000 (1-5).

There are 2 types of BA that are currently recognized and described: a fetal or embryonic type and a perinatal type. The fetal type occurs in 15-35% of cases and is characterized by an earlier onset of cholestasis (1). There is an association between the fetal type and other congenital anomalies such as situs inversus, polysplenia, cardiac malformations, and other manifestations (1,2). There also tends to be a lack of bile duct remnants at the porta hepatis with the fetal form of BA. The more common form of BA is the perinatal form which occurs in 65-85% of cases and is not associated with congenital anomalies (1).

As the names imply, the initiating event of the two types are theorized to occur at different times in development with probably very different etiologies. Research has focused on the possible etiology of the perinatal form with causes including viral infections, auto-immune disease, and immune mediated damage (1,4). The viruses that are under question include CMV, reovirus, rotavirus, HPV, and retroviruses (4). Theories of the etiology of the fetal type of BA center around a possible morphogenesis defect, known as the ductal plate malformation, due to defective gene expression leading to the associated congenital anomalies (1,4). While there are possible candidates for the defective gene there has been no definitive identification. Therefore the etiology of both forms of BA remains unknown at this point.

The signs and symptoms of biliary atresia will be dependent upon the time of presentation. Usually, the patient is born at term with a normal birth weight. Jaundice can be present at birth or it can present as late as 3 to 5 weeks of life. Other than jaundice, another common complaint is acholic stools, which are highly suggestive of cholestasis. There can be some pigment in the stool due to sloughing of cells that contain pigments. However, this pigment is only present superficially with the core of the stool remaining pale (3). Since the bile pigments are no longer released into the stool, they will be deposited in the urine leading to darker urine.

On physical exam the patient will usually have an enlarged firm liver (normal averaging 4.5-5 cm at 1 week and 6-7 cm during early adolescence) (3). The presence of splenomegaly is variable and more common with later presentations as part of the constellation of portal

hypertension. Patients may also present with the findings associated with the fetal form of BA including polysplenia, situs inversus, and cardiac malformations (1).

The undiagnosed infant with BA will present with a much different picture. This is due to the progressive nature of the disease. Later presentations are associated with the progression of the disease to biliary cirrhosis and the development of portal hypertension with failure to thrive (2). The clinical picture at this point will be dominated with findings suggestive of cirrhosis and portal hypertension such as jaundice, hepatosplenomegaly, a nodular liver, varices, ascites, and hepatic vascular bruits (1,3).

Laboratory examination will show an elevated total bilirubin with an increased direct (conjugated) portion. The serum aminotransferases levels will tend to be normal or mildly elevated. Alkaline phosphatase will be highly elevated reaching levels higher then 5 times normal (2). Early in the disease process there are usually no changes in coagulation studies.

There are many conditions that can cause cholestasis in the neonate and lead to jaundice. These include hepatitis (viral and other causes), sepsis, endocrinopathies, metabolic derangements, and nutritional hepatotoxicities (6). The most common disorders in decreasing incidence are idiopathic neonatal hepatitis, BA, alpha-1-antitrypsin deficiency, and persistent intrahepatic cholestasis disorders (2). The greatest challenge is the differentiation of BA from idiopathic neonatal hepatitis and the intrahepatic cholestasis disorders.

Idiopathic neonatal hepatitis is not the same entity as neonatal viral hepatitis. As its name implies, the cause is unknown. There have been diseases that are now described that were once under the heading of idiopathic neonatal hepatitis such as alpha-1-antitrypsin deficiency. These patients tend to present with low birth weight, early onset of jaundice, and usually have pigmented stools (2). Associated malformations are usually not found with this disease and if present should prompt the search for an alternate diagnosis. Laboratory findings include elevations in the serum aminotransferases and bilirubin. Alkaline phosphatase can be elevated but is not always. Coagulation studies may also be abnormal. A diagnosis of idiopathic neonatal hepatitis should only made when other causes of cholestasis (including BA and alpha-1-antitrypsin deficiency) are ruled out. Histologic findings include disruption of the lobular architecture with hepatocellular swelling, focal necrosis, and the presence of multi-nucleated giant cells (2,7). However, the presence of hepatocellular swelling giant cells can also be seen in BA (7). The largest portion of the workup for idiopathic neonatal hepatitis is to rule out any metabolic, infectious, genetic, or other described conditions.

Under the heading of persistent intrahepatic cholestasis disorders is intrahepatic bile duct paucity which includes both non-syndromic bile duct paucity and syndromic forms such as Alagille syndrome. These are characterized by the absence or marked decrease in the number of intrahepatic interlobular bile ducts, with normal sized arteries and portal veins in the triad. Intrahepatic bile duct paucity was previously referred to as "intrahepatic bile duct atresia" or "intrahepatic biliary atresia" (6, 8). This was a misleading term that is no longer used since by definition BA is the fibrosis and obliteration of the extrahepatic biliary system, not the intrahepatic system. These diseases are diagnosed by the presence of cholestasis and bile duct paucity on liver biopsy. The non-syndromic form describes a common pathology with various etiologies, which are still poorly understood. With the syndromic forms there are characteristic findings associated with the bile duct paucity (8). For example in Alagille syndrome, or arteriohepatic dysplasia, there are characteristic facies along with ocular, cardiovascular, vertebral, and kidney pathology.

Efforts must be made to diagnose BA early since the success of intervention is dependent upon the time frame. When a child presents with jaundice, the first step is to evaluate the total and fractionated bilirubin in each patient with jaundice. If the elevation is isolated to the unconjugated (indirect) fraction of bilirubin then significant liver pathology is unlikely (3). However, if the elevation is in the conjugated (direct) fraction or it is 20% or greater of an elevated total bilirubin then cholestasis more likely (6). If the presence of cholestasis is established, then the etiology must be found in a timely fashion. Panels of testing can quickly rule out or diagnose entities such as hypothyroidism, galactosemia, tyrosinemia, alpha-1-antitrypsin deficiency, and infectious diseases. Once these items are ruled out, the challenge is to differentiate between idiopathic neonatal hepatitis and BA.

Non-invasive testing for biliary atresia currently relies on the use of hepatobiliary scintigraphy with the use of 99mTc-iminodiacetic acid compounds or HIDA scans. The newer iminodiacetic compounds have greater concentrations in the bile then the original compounds. HIDA scans using older compounds will not visualize the biliary tract if the bilirubin is high, so the currently favored compound is 99m Tc-disofenin or DISIDA. Images consistent with BA will show normal uptake by the liver with no excretion into the bowel even after 24 hours. The specificity of the DISIDA scan can be increased by pretreatment with phenobarbital (5mg/kg/24h PO for 5 days prior to study) to increase the excretion of the disofenin (6,9). If the DISIDA scan demonstrates bile flow from the liver to the duodenum (i.e., the biliary tree is visualized), then BA is ruled out and the work-up can stop. Patients who demonstrate an obstructive pattern on DISIDA will have BA in 80-85% of cases (10); however, neonatal hepatitis is still possible since it can cause severe cholestasis. In patients with idiopathic neonatal hepatitis, there is slow uptake of the compound with excretion into the bowel; however, in some instances, the cholestasis is so sluggish, it cannot be reliably distinguished from BA. DISIDA scanning is less reliable with higher levels of serum bilirubin, however bowel activity is still observed with hyperbilirubinemia as high as 20-30 mg/dL. If there is poor uptake by the liver without bowel activity it is indicative of severe hepatocyte damage that could be caused by either BA or idiopathic neonatal hepatitis (9).

Another method for the diagnosis of BA is the use of ultrasound guided liver biopsy. While there are no pathognomonic histological changes, the biopsy is reported to provide a diagnosis of BA ranging from 70% to 97% (3,7). Findings include edema of the portal tracts, tortuous proliferation of bile ductules, fibrosis, along with intracellular and canalicular cholestasis. There is also a mixed infiltration of neutrophils and lymphocytes with a mild non-specific cholangitis (7). Of note is that there can also be ballooning of the hepatocytes and multinucleated giant cell formation. This can cause some overlap between the histological picture presented by BA and by idiopathic neonatal hepatitis (2,7). If the biopsy shows absence or reduction in the amount of interlobular bile ducts at the portal triad, with an intact biliary tree on scintigraphy, then a diagnosis of intrahepatic bile duct paucity (formerly known as intrahepatic biliary atresia) is established and true or extrahepatic BA is ruled out (6). Also of note is that there should be no dilation of the intrahepatic bile ducts in BA as can happen with some other forms of extrahepatic cholestasis (11).

The gold standard for the diagnosis of BA is the laparotomy with intraoperative cholangiography. If an intact extrahepatic biliary system is not visible, then extrahepatic biliary atresia is evident. If an intact biliary tree is visible, then an intraoperative cholangiogram is done, in which the surgeon cannulates the bile duct and injects contrast to determine if the biliary ducts are patent. Non-patency indicates sclerosed ducts and extrahepatic biliary atresia. A patent biliary system visualized on the intraoperative cholangiogram rules out extrahepatic biliary atresia. At this point, a wedge liver biopsy is obtained. This biopsy is examined for the presence of intrahepatic bile ducts. If the intrahepatic bile ducts are obliterated or reduced in number, then bile duct paucity (formerly called intrahepatic biliary atresia), is present. An intact and patent extrahepatic biliary tree rules out extrahepatic biliary atresia and the presence of normal intrahepatic bile ducts rules out bile duct paucity. This diagnostic algorithm is summarized below.

Diagnostic algorithm of biliary atresia:

1) Direct hyperbilirubinemia prompts evaluation and lab work-up.

2) Look for evidence of bile excretion (DISIDA scan, pigmented stools): Any evidence of bile excretion, rules out BA. If cholestasis is present (i.e., no bile excretion is demonstrated), then proceed to next the step.

3) Laparotomy:

a) Look for a visible biliary tree: If absent, then extrahepatic BA is present. If present, then proceed to next step.

b) Perform an intraoperative cholangiogram: If non-patent, then extrahepatic BA is present. If cholangiogram demonstrates patents ducts, then proceed to next step.

c) Perform a wedge liver biopsy: If intrahepatic bile ducts are obliterated or reduced in number, then bile duct paucity (formerly known as intrahepatic BA), is present. The biopsy can also be used to find an alternate diagnosis. If bile ducts are patent and present, then BA is not present, in which case the biopsy is likely to demonstrate an alternate diagnosis such as neonatal hepatitis.

Depending on the anatomic type of BA which is present, it can be classified as either a correctable lesion (20% of cases) or a non-correctable lesion (80% of cases) (2,10). A correctable lesion has fibrosis of the distal biliary tree with the proximal biliary tree and the intrahepatic bile ducts remaining patent. In these cases, excision of the fibrotic area and direct drainage into the bowel is possible.

In the non-correctable lesions, the biliary system is fibrotic to the level of the porta hepatis. These patients need to undergo the Kasai procedure to establish bile flow. The Kasai procedure is the Roux-en-Y hepatoportoenterostomy where the porta hepatis is attached to a loop of bowel after resection of the fibrotic biliary system. This procedure basically anastomoses the liver directly to the bowel so that in theory, bile can flow from the liver into the bowel. The reason that the procedure succeeds is that at the porta hepatis there are microscopic bile ductules that have proliferated which communicate with the intrahepatic system. Some groups use frozen section biopsy during the laparotomy to examine the tissue at the porta hepatis using the size of the vessels as a marker for the likelihood of successful re-establishment of bile flow. However, there have been variations in the size of vessels required and this theory is not universally accepted.

The success of the Kasai procedure depends largely on 2 factors: age at procedure and experience of the center it is performed at. To obtain maximum benefit from the Kasai procedure it should be performed before the patient is 3 months old, ideally less then 2 months. This is the major reason why the diagnostic determination of whether BA exists, must be done expeditiously. Establishment of bile flow is achieved in 80% of the patients who are less then 2 months, 50% between 2 and 3 months, and less then 10% if older then 3 months (12). The decrease in the success rate of the Kasai procedure with advancing age is due to progressive damage to the liver from untreated BA (i.e., further back-up of bile flow inflicts additional damage to the existing intrahepatic ducts). The other factor is the experience of the center performing the surgery. Outcomes of the procedure and post-procedure survival are improved when the hospital does more then 5 procedures a year (1,5,13).

If the child is diagnosed at an age greater then 3 months, the Kasai procedure has a low probability of success. Performing a Kasai procedure after this age is thus controversial, versus proceeding straight to liver transplantation, which is the treatment for a failed Kasai procedure. It is the general consensus that a patient should undergo the Kasai procedure even if they present at ages greater then 3 months if it is possible that bile flow can be established (12,14). While a post Kasai transplant is technically more difficult, there was no reported change in survival after transplantation in patients who underwent primary transplantation versus those who had a failed Kasai procedure prior to transplantation (11,13). The use of the Kasai procedure may not provide long term cure in the older BA patient but it may buy time for preparation for transplantation, finding a donor, and advancement of transplantation technology.

Ascending cholangitis is the most common complication, occurring in 40-60% of Kasai procedures (1). The etiology for this is anatomic and bacterial. Bowel bacteria have access to the existing bile ducts and hepatic tissue. The normal anatomy of an intact bile duct prevents bowel contents from refluxing up toward the liver. In the Kasai procedure, the bowel contents containing digestive enzymes have direct access to the existing bile ducts and hepatic tissue causing the cholangitis. An anti-refluxing valve can be surgically created within the duodenal segment anastomosed to the liver, but such alterations in the Kasai procedure and various medical regimens have not proven successful. There does appear to be an increased risk in the patients with established bile flow, probably due to an intact pathway for ascending bacteria. Prophylactic antibiotics with trimethoprim-sulfamethoxazole is designed to reduce bowel bacterial counts. Repeated episodes of cholangitis can lead to extensive liver damage and cirrhosis.

Another common complication of BA is portal hypertension, which occurs in 35-75% of patients (1). This occurs due to the progressive inflammation and fibrosis of the intrahepatic biliary system and/or repeated episodes of cholangitis leading to cirrhosis. The portal hypertension that develops will have the sequelae of other forms of portal hypertension such as varices, ascites, hypertensive gastropathy, hypersplenism, and encephalopathy (1). The most common presentation is esophageal variceal hemorrhage occurring in 30-60% of patients (1). Treatment relies on the same methods employed in adults for other forms of portal hypertension.

BA is a chronic cholestatic disease if untreated can lead to complications as a result of the cholestasis. The end result is biliary/hepatic cirrhosis if BA is not treated with a life expectancy of 2 years (2). Mortality is a result of liver failure or portal hypertension. As mentioned before the chance of establishing bile flow in BA patients with the Kasai procedure is dependent upon the age that the patient undergoes surgical intervention. However, it should be noted that the establishment of bile flow does not necessarily mean long term cure since BA also involves intrahepatic inflammation that can lead to cirrhosis.

After the Kasai procedure, the patient can be stratified into 1 of 3 prognostic groups at 4 to 6 weeks post operatively (10). The first group are the patients who produce adequate bile flow and are relieved of their jaundice. They will have long term survival and possibly not need liver transplantation. The second group has moderate bile flow but they remain jaundiced and will continue to survive post-Kasai, however they will eventually need liver transplantation later in life. The third group are those who do not establish bile flow. This is considered a failure of the Kasai procedure and they will need liver transplantation in order to survive.

While the Kasai procedure establishes bile flow, it does not necessarily halt the intrahepatic inflammation and fibrosis. Patients who undergo the Kasai procedure can survive with their native liver in 20-30% of cases, but the remainder will eventually need liver transplantation (2,10). Overall survival rates of patients with BA post intervention in recent studies range from 70 to 85% (5,13). Ten year survival ranges from 33% in older studies to 68% in more recent studies (2,13). Survival with one's native liver at 5 years has been reported to be as high as 32% in recent studies and 27% at 10 years (5,13).

Biliary atresia is no longer a fatal disease in all who are diagnosed with it. The early diagnosis and treatment of BA can lead to long term survival without the need for liver transplantation. However, the key is the early diagnosis of BA in order to ensure that surgery can be performed in a timely manner at a high level center to increase the likelihood of success. Despite this, there are still many children who are untreated at 3 months of age (as high as 14-19% in some studies) (1). Efforts to introduce screening methods for BA have been

attempted with poor results. The best method so far, is to maintain a high clinical suspicion in the jaundiced patient. Direct hyperbilirubinemia deserves a prompt and thorough evaluation.

Questions

1. True/False: A 2 week old infant presents with persistent jaundice to the office. No further work up is necessary since this is physiologic jaundice.
2. A DISIDA scan report, for a patient in whom biliary atresia is suspected, comes back stating that there was poor uptake into the liver and no visualization of the isotope into the bowel. Can you diagnose biliary atresia in this patient?
3. A liver biopsy shows hepatocellular ballooning and the presence of multinucleated giant cells. Is this consistent with biliary atresia?
4. A patient presents to you with lightly colored stool; however, when the stool is broken up it is noticed that the center is clay colored. What is this indicative of?
5. A 16 week old patient is diagnosed with biliary atresia, should he/she undergo a Kasai procedure if there are no contraindications or should the patient just wait for a liver transplant?

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Answers to questions

1. False. Persistent jaundice needs to be worked up before permanent damage is done by any number of pathological conditions, such as BA. Since there is little risk involved, the threshold to obtain a serum fractionated bilirubin should be low. If there is an elevation of conjugated bilirubin at 14 days of age or earlier, it is by definition neonatal cholestasis.
2. No. With poor uptake into the liver you can only state that there is cholestasis. This may be transient cholestasis due to hepatitis, or it may be due to severe damage to the hepatocytes by several possible causes including biliary atresia. To make a diagnosis, there needs to be normal uptake in the liver with no movement into the bowel, even after 24 hours. Pretreatment with phenobarbital improves the yield on the DISIDA scan.
3. Yes, this histopathology is consistent with the histopathology seen with biliary atresia. However, it is also consistent with idiopathic neonatal hepatitis and therefore a definitive diagnosis can not be made on this biopsy result alone.
4. The presence of clay colored or acholic stools are indicative of cholestasis. The lack of bile flow into the bowel prevents the characteristic stool coloring. The superficial light coloring is due to the sloughing of pigmented cells during the transit in the bowel and does not affect the core of the stool.
5. While there is little chance of long-term survival with the patient's native liver in someone who undergoes the Kasai procedure after 3 months of age, there is some benefit. The Kasai procedure can lead to extended survival time with the native liver, allowing the patient to stabilize baseline health. There is also a benefit in that there will be longer period of time to find a donor and prepare the patient for transplantation. However, each patient is different and some may be better served by primary liver transplantation.

Chapter IX.5. Hepatitis
Vince K. Yamashiroya, MD

This is a 14 year old Caucasian patient who comes to your office with a chief complaint of nausea, poor appetite, and fever for one week. Her fever has been between 101 and 102 degrees, and occurs every day. She had two non-bloody, non-bilious episodes of emesis in the last two days and also has abdominal pain on her right side below the ribs, which has been getting worse. Her urine color is darker than normal, although she has not been drinking much fluid. She denies any coughing, URI symptoms, diarrhea, and dysuria. She is not sexually active and denies drug or alcohol use. She is not taking any medications other than ibuprofen for her fever.

Exam: T38.4, P85, R16, BP 100/70. She has a 2.3 kg (5 pound) weight loss since her last visit 6 months ago. She appears tired and ill-appearing, but is cooperative with her examination. Her skin is jaundiced and there is scleral icterus. Her liver edge is palpable 5 cm below the right costal margin, and is moderately tender. There is no splenomegaly. The rest of her examination, including ophthalmologic, cardiac, pulmonary, and neurological systems, is normal. She has no lymphadenopathy.

Laboratory data: Normal CBC and reticulocyte count. Electrolytes, BUN, and creatinine normal. AST 500, ALT 550, alkaline phosphatase 500, GGT 50, total bilirubin 13.5 (direct fraction 5.0). Prothrombin time is 14.0 seconds (prolonged).

In light of her presentation, additional blood work is sent for anti-HAV IgM, HBsAg, anti-HBc, and HCV. On further questioning, it is discovered she ate at a restaurant one month ago where a worker was found to have hepatitis A. Her blood work later returns positive for hepatitis A.

The liver performs many essential functions. It is the first to receive blood from the intestines through the portal vein. It stores vitamins B12, A, D, E, and K. It also stores glucose in the form of glycogen, or converts it into fatty acids. It deaminizes amino acids into ammonia, which is then converted into urea. It manufactures proteins such as albumin, prothrombin, fibrinogen, transferrin, and glycoprotein from amino acids. The cytochrome P-450 system is responsible for the detoxification of many different compounds (e.g., drugs), and is important in the metabolism of steroid hormones and fatty acids. It also synthesizes bile and plays an important role in lipid metabolism. It excretes bilirubin and biliverdin formed from heme in red blood cells from the reticuloendothelial system in different parts of the body (1). Therefore, diseases that damage the liver can have a very detrimental effect on the body. This chapter will discuss some of the diseases that affect the liver, focusing on viral hepatitis.

Hepatitis is an inflammation of the liver and can be due to many different causes. Although viral hepatitis is well known, other diseases include autoimmune causes such as systemic lupus erythematosus, drug-induced causes such as isoniazid, and metabolic disorders such as Wilson disease, alpha-1-antitrypsin deficiency, tyrosinemia, Niemann-Pick disease type 2, glycogen storage disease type IV, cystic fibrosis, galactosemia, and bile acid biosynthetic abnormalities (2). The anatomy and physiology of the liver is complex and outside the scope of this chapter, although its basic concepts are important to understand the pathophysiology of liver disease. The common theme is that there is injury or death to the hepatocytes. When this occurs, enzymes in these cells are released, which include the aminotransferases (aspartate aminotransferase and alanine aminotransferase), alkaline phosphatase, and gamma-glutamyl transpeptidase (GGT). It should be noted that these aminotransferases are also located in heart and skeletal muscle tissues, although alanine aminotransferase (ALT) is more specific to the liver than aspartate aminotransferase (AST) and has a longer plasma half-life (which makes an elevation of AST indicative of early hepatic damage). Alkaline phosphatase, besides being found in the liver, is also present in kidney, bone, placenta, and intestine. GGT is found in biliary epithelia and hepatocytes, and is therefore a more specific marker for liver disease (3). A misnomer is that liver function tests (LFT's) consists of measuring the levels of aminotransferases, alkaline phosphatase, and GGT. However, these intracellular liver enzymes are not indicative of liver function, but rather damage to the liver. As was mentioned earlier, the liver has many functions, such as the production of proteins from amino acids, gluconeogenesis and glycogenolysis, and the excretion of bilirubin. Therefore, damage to the hepatocytes will result in decreased production of proteins, notably albumin, prothrombin, fibrinogen, glycoproteins, lipoproteins, and enzymes. Low albumin can result in ascites, and low prothrombin, fibrinogen, and other clotting factors can lead to a hypocoagulable state. Hypoglycemia can result from failure of the damaged hepatocytes in maintaining glucose homeostasis (4). A major function of the hepatocyte is the conjugation of bilirubin and its excretion into the bile canaliculi. A sign of hepatic injury is not elevated unconjugated bilirubin, but rather conjugated hyperbilirubinemia, which may be due to the decreased excretion of conjugated bilirubin (cholestasis) due to inflammation around the canaliculi. The build up of bilirubin in the bloodstream leads to jaundice or icterus, which is a yellow coloring of the skin and sclera (of note, scleral icterus can be seen when the bilirubin level exceeds 2.5 mg/dl) (5). Note that only some patients with hepatitis are jaundiced because only some patients develop cholestasis. Ammonia is a normal byproduct of protein degradation by intestinal bacteria, of deamination processes in the liver, and glutamine hydrolysis in the kidneys. The liver metabolizes this toxic ammonia into urea by the Krebs-Henseleit cycle. With hepatic injury, however, the ammonia may accumulate which can lead to encephalopathy and coma (6).

With this short explanation on the pathophysiology of hepatic parenchymal injury, the diseases that cause hepatitis can be more readily understood. This next section will focus primarily on viral hepatitis, in addition to two major causes of metabolic diseases of the liver: Wilson disease and alpha-1-antitrypsin deficiency.

The viral causes of hepatitis can be divided into hepatotropic and non-hepatotropic viruses. The non-hepatotropic viruses include measles, rubella, enteroviruses (coxsackie and echo), flaviviruses (yellow fever, Dengue fever), filoviruses (Marburg and Ebola), arenaviruses (Lassa fever), parvovirus B19, adenovirus, and herpesviruses (herpes simplex types 1 and 2, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and human herpes virus type 6) (7). The hepatotropic viruses are fewer in number and consist of hepatitis A, B, C, D, E, and G. The hepatitis viruses important in clinical medicine are hepatitis A, B, C, and delta.

Hepatitis A (HAV) is a picornavirus (single-stranded RNA virus) and is transmitted via the fecal-oral route. After it is ingested, it replicates in the small intestine, and then travels to the liver via the portal vein, where it attaches to hepatocytes via a receptor on the hepatocyte membrane. The replicated HAV is then excreted in the bile and passed on in the feces. Liver injury is thought to be due to a T-cell mediated destruction of hepatocytes, rather than to a direct cytotoxic effect. Important risk factors for acquiring HAV infection are close contact (including sexual), fecal-oral (i.e., poor hand washing, etc.), travel to developing countries, and intravenous drug abuse. Therefore, parenteral transmission of HAV is possible, although uncommon. The incubation period of HAV is 15 to 40 days, with a mean of 28 days, after which the patient can develop clinical manifestations of hepatitis. In older children and adults, symptoms can include fever, anorexia, nausea and vomiting, right upper quadrant abdominal pain, dark urine, and jaundice. Less common symptoms include headache, myalgias, arthralgias, pruritus, and rash. Signs can include hepatosplenomegaly, leukopenia, cervical lymphadenopathy, hyperbilirubinemia, and elevation of serum aminotransferase levels. Fulminant hepatic failure is rare. In infants and younger children,

HAV can be asymptomatic or present with "stomach-flu symptoms" of nausea, vomiting, and diarrhea without icterus; therefore suspicion of hepatitis in these patients is often low. Diagnosis is made by measuring anti-IgG and anti-IgM HAV titers. Anti-IgM is present in the acute period, peaking at 1 week and disappearing 3 to 6 months later. Anti-IgG appears later and is highest at 1 to 2 months and lasts for years, and therefore signifies convalescence or immunity. The treatment for HAV is mainly supportive, and the prognosis is good in that it is acute and self-limiting. It does not lead to chronic hepatitis or chronic carriage. In a small percentage of patients, HAV infection can be relapsing or protracted. Prevention consists of good hygiene, the administration of immunoglobulin prophylaxis to contacts, and active vaccination (8,9). Intramuscular immunoglobulin when given as postexposure prophylaxis has >85% effectiveness in preventing symptomatic infection if given in the first 2 weeks of exposure; however, its immunity is short-lived. Active HAV vaccination is recommended for preexposure prophylaxis to people traveling to foreign countries with a high rate of HAV (excludes Australia, Canada, Japan, New Zealand, Western Europe, and Scandinavia). Other recommendations for vaccination are children living in areas of the United States with an incidence rate twice the national average (which includes Arizona, Alaska, Oregon, New Mexico, Utah, Washington, Oklahoma, South Dakota, Idaho, Nevada, and California), people with chronic liver disease, homosexual and bisexual men, IV drug users, patients with clotting-factor disorders, and those who are at risk for occupational exposure) (10).

Hepatitis B (HBV) is a DNA virus in the family hepadnaviridae and has a unique structure. It consists of two shells, of which the outer shell contains the hepatitis B surface antigen (HBsAg) and the inner shell contains the hepatitis B core antigen (HBcAg). In the core are the viral DNA and the hepatitis B e antigen (HBeAg) which is a derivative of the precore DNA region of the HBcAg gene. Like the hepatitis A virus, it has a high affinity for hepatocytes and causes destruction through T-cell mediated cell destruction. HBV is transmitted parenterally and is found in all bodily fluids, but is not found in feces. Although it is found in saliva, the chances of acquiring HBV through sharing of toys by young children are small. Sexual intercourse and vertical transmission (from mother to infant) are other important routes of transmission. Vertical transmission, which is a major cause of acquiring HBV in endemic countries, can occur through the infant swallowing maternal blood during birth or transplacentally. In addition, infants who acquire HBV perinatally have a high risk for chronic hepatitis infection, cirrhosis, and hepatocellular carcinoma. The incubation period is from 50 to 180 days. The clinical course has three stages: prodromal (incubation) stage, symptomatic (icteric) stage, and convalescent stage. The prodromal stage lasts for 2 to 3 weeks and although in most cases the patient is asymptomatic, it can rarely present with membranous nephropathy and vasculitic syndromes. This is followed by the symptomatic (icteric) stage that consists of fatigue, fever, myalgias, anorexia, pruritus, nausea, vomiting, and abdominal pain. This stage can last for 4 to 6 weeks. An interesting dermatologic phenomenon that can occur is papular acrodermatitis of childhood (Gianotti-Crosti syndrome), which presents as nonpruritic symmetrical lichenoid papules on the face, buttocks, and extremities that last for 2 to 3 weeks and often preceded by lymphadenopathy, hepatomegaly, and occasionally splenomegaly (11). The extrahepatic manifestations are possibly due to immune complexes of HBsAg and anti-HBs. After this stage is the convalescent stage (8).

The diagnosis of HBV is made by interpretation of serological markers of HBsAg, HBeAg, anti-HBe, anti-HBc, and anti-HBs, (note the absence of HBcAg which can only be assayed on a liver biopsy, since it does not circulate in the blood in appreciable quantities) and the patient's clinical state. It would be helpful to look at a graph of these markers and course of disease for a visual depiction. However, these graphs are confusing to most students so it would be better to understand where these markers are from and their immunologic/clinical consequence. After inoculation, viral replication occurs. So during incubation and replication of the virus, one would find viral antigens in the serum, namely HBsAg and HBeAg. In fact, these antigens are not found in the blood until 1 to 3 months after the person becomes infected. Patients with these circulating antigens are potentially contagious. A positive HBsAg together with a positive HBeAg is associated with a higher degree of contagiousness than a positive HBsAg alone. While the patient has these antigens then, he is infected and is either in the incubation or symptomatic stage of the disease (acute or chronic). In the meantime, the immune system is fighting off this infection with the production of antibodies against these antigens. For example, Anti-HBs is made in response to HBsAg. The antibody and antigen should not be detectable in the blood stream simultaneously. Basically, the presence of HBsAg indicates infection and contagiousness, while the presence of anti-HBs indicates the presence of immunity. However, there is a brief period after the HBsAg declines and before the anti-HBs rises, when both of them are non-detectable (negative), which is called the "window phase". Anti-HBc is always positive during this window phase.

In acute HBV infection, HBsAg and HBeAg are present. If recovery and immunity are to follow, both antigen levels decline as anti-HBc and anti-HBe levels rise. Ultimately, the presence of anti-HBs signifies immunity. In chronic HBV infection, HBsAg persists and anti-HBs fails to develop. Once anti-HBs and/or anti-HBc are present, these can be fractionated to IgM and IgG. IgM signifies an early immune response, while IgG signifies a later or booster response. It may be best to understand these antigens and antibodies in relation to specific clinical questions.

Is the patient immune or contagious? If the HBsAg is positive, the patient is contagious. If the HBsAb is positive, the patient is immune.

Is a pregnant mother at risk for passing HBV to her child at birth? If mother's HBsAg is positive, then perinatal transmission of HBV is possible and the newborn must receive HBV prophylaxis. If the HBsAg is negative, there is no risk.

The patient is contagious (i.e., the HBsAg is positive), but how contagious is he? If the HBeAg is positive, he is very contagious. If the anti-HBe is positive, then he is less contagious.

Has the patient been exposed to HBV in the past? Check the HBsAg, anti-HBc and anti-HBs. If all of these are negative, the patient has never been exposed to HBV. If one or more are positive, then the patient has been exposed to HBV.

A hepatitis B vaccine recipient wants to confirm immunity. If the anti-HBs is positive, he is immune. If not, immunity has not yet developed.

The prognosis of HBV infection is variable and depends on immune and genetic factors, the age of the patient, and serologic stage of infection. The risk for chronicity increases when primary infection is acquired in the neonatal period compared to adults. For instance, 95% of neonates become chronic carriers, compared to 20% of children, and less than 10% of adults. Chronic states can range from chronic active hepatitis to a chronic non-symptomatic carrier state. Also, the risk for hepatocellular carcinoma (HCC) increases with chronicity; therefore, patients who develop HBV in the neonatal period have the highest risk of developing liver cancer compared to other age groups. It has been shown that men who develop HBV at birth have a 50% lifetime risk for developing HCC compared to women who have a 20% lifetime risk. Patients who develop HCC have a poor prognosis, which has a less than 5% 5-year survival rate (8).

Fortunately, the risk of HBV has declined with universal immunization and diligent prenatal screening. Infants who are born to HBsAg-negative women are given the routine 3-dose hepatitis B immunization, with preterm infants given the first dose after they reach 2 kg. However, newborns from HBsAg-positive women are given both the hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) as postexposure prophylaxis within 12 hours of birth regardless of their birth weight. For infants less than 2 kg, the initial dose should not be

counted in the 3-dose schedule (i.e., they are given 4 doses). After completion of the HBV vaccine series, these infants born to HBsAg positive mothers should be tested serologically for anti-HBs and HBsAg 1-3 months after the last dose. For infants who have low anti-HBs (<10 mIU/ml) and negative HBsAg, they should receive 3 additional doses of vaccine at a 0, 1, and 6-month schedule, with anti-HBs testing done 1 month later to determine immunity. If the HBsAg status of the mother is unknown, serologic testing on the mother should be performed as soon as possible. Term infants should receive the hepatitis B vaccine within 12 hours of birth. HBIG does not need to be given unless the mother's serology returns as being HBsAg positive, in which case HBIG is given soon after. Two hepatitis B vaccines are currently available (Recombivax and Engerix). The schedule consists of 3 doses, with the first dose being given soon after birth, a second dose at least 1 month later, and the third dose when the infant is at least 6 months old or at least 2 months after the second dose and at least 4 months after the first dose (12,13). HBV vaccine is also available in a combination vaccine with diphtheria-tetanus-pertussis (DTaP) and inactivated polio vaccine (IPV).

Hepatitis C was a major cause of post-transfusion hepatitis in the past and was known as non-A, non-B hepatitis prior to the late 1980's. It belongs to the family flaviviridae, which are enveloped RNA viruses. It is spread parentally with highest risk factors being illicit intravenous drug use and unprotected sexual intercourse. Although it is an important cause of posttransfusion hepatitis, only 5 to 10% of HCV infections are due to transfusions. Another risk factor is needlestick injuries in hospital workers. Vertical (perinatal) transmission is probably the most common cause of HCV in children, although overall, it is uncommon for an infant to acquire HCV compared to HBV. HCV is thought to have a direct cytotoxic effect, which is in contrast to HAV and HBV. Clinical manifestations are the same for the other forms of hepatitis B, with most cases being anicteric. However, unique features are fluctuating or polyphasic levels of aminotransferases during the course of disease and slow resolution. In 50% of individuals, chronic HCV infection can occur. Out of this 50%, half become chronic carriers and the other half progress to chronic active infection or chronic persistent infection. For those who are chronic carriers, they are asymptomatic although test positive for HCV. For those who develop chronic infection, 20% will develop cirrhosis and are at high risk for hepatocellular carcinoma. There is no vaccine available against HCV due to its high rates of mutation in its viral envelope, although children who do develop HCV infection have been treated successfully with interferon alpha (8,14).

Hepatitis D virus (HDV) or delta agent is a satellite virus, meaning that it can only cause disease, not by itself, but in conjunction with another virus, which in this case is hepatitis B virus. HDV is a very small RNA virus and is thought to damage hepatocytes by a direct cytotoxic effect. Like HBV, it is spread parenterally. Unfortunately, those patients with HBV who are co-infected with HDV have severe forms of hepatitis. Mortality is higher at 2% to 20% compared to less than 1% for those with only HBV infection. Most patients (about three-quarters) with chronic HDV infection develop cirrhosis and portal hypertension (8).

Two forms of metabolic liver diseases will be discussed next: Wilson disease and alpha-1-antitrypsin deficiency. Wilson disease or hepatolenticular degeneration is a disease of copper metabolism. It is autosomal recessive with the affected gene, ATP7B, being on the long arm of chromosome 13. It occurs worldwide, with a prevalence of about 1 in 30,000, with higher rates in consanguineous families. Mutations in this gene cause impaired copper excretion from the hepatocyte to bile, and decreased incorporation of copper into ceruloplasmin in the hepatocyte leading to high serum copper levels and deposition of copper in many organs. The clinical manifestations of Wilson disease rarely appear until 5 years of age, at which time the gradual build up of copper in various organs becomes symptomatic. Dangerous levels of copper become present in the liver, nervous system, cornea, kidneys, and other organs leading to hepatitis, neuropsychiatric symptoms (some of which are tremor, clumsiness, ataxia, headaches, seizures, and dementia), and Kayser-Fleischer rings around the corneas (a greenish-brown ring in Descemet's membrane at the periphery of the cornea). The diagnosis is made on the basis of several tests and clinical data. Serum ceruloplasmin is low (<20 mg/dl), hepatic copper concentration is high (>250 mcg/gm of dry wt.), 24-hour urine copper excretion is high (>100 mcg/24 hours), Kayser-Fleischer rings are present, and incorporation of 64Cu into ceruloplasmin is low. Without treatment, Wilson disease is fatal; therefore, the basis of therapy targets the reduction of stored copper and preventing reaccumulation of copper. This is done by using copper-chelating agents (e.g., D-penicillamine, trientine, zinc acetate, ammonium tetrathiomolybdate, and vitamin D), a low copper diet, oral zinc therapy, and possibly antioxidants (15).

Alpha-1-antitrypsin deficiency (A1AT deficiency) is another important metabolic liver disease that is autosomal recessive and occurs in 1 in 1,600 to 2,000 live births. Alpha-1-antitrypsin is a glycoprotein that inhibits neutrophil proteases such as neutrophil elastase, cathepsin G, and proteinase 3. The absence of alpha-1-antitrypsin allows these dangerous enzymes to cause damage to organs. The two organs that are affected are the liver and lung. Hepatic manifestations include prolonged jaundice in infants; neonatal hepatitis syndrome, and mild elevations of aminotransferases in toddlers; portal hypertension and severe liver dysfunction in older children; chronic hepatitis, cryptogenic cirrhosis, and hepatocellular carcinoma in adults. The pulmonary manifestation is emphysema, although this commonly occurs in adult cigarette smokers and rarely in children. A1AT deficiency is suspected in infants with neonatal jaundice or older children and adults with unexplained chronic liver disease. The diagnosis is made by determining the phenotype of serum alpha-1-antitrypsin by electrophoresis or isoelectric focusing, and confirmation by liver biopsy. The phenotype associated with liver disease is an individual homozygous for PiZZ (ZZ phenotype of the protease inhibitor system). The treatment of liver disease is by liver transplantation, and emphysema with lung transplantation and cessation of cigarette smoking. Gene therapy may be possible in the future (16, 17).

Lastly, the work-up of hepatitis should be done in a systematic and stepwise fashion. Initially, a complete blood count, total and fractionated serum bilirubins, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and prothrombin time (PT) should be performed. AST, ALT, and GGT assess for hepatocellular damage (one could argue that only one of these is necessary) and PT is the most useful test to determine if liver dysfunction is present. If these tests are abnormal and the etiology is unknown, viral hepatitis titers consisting of anti-HAV IgM, HBsAg, anti-HBc, and anti-HCV should be performed. If these tests are negative, other viruses such as Epstein-Barr virus and cytomegalovirus should be considered. If these tests are still negative, other etiologies should be sought after. These etiologies include biliary atresia in neonates (refer to the chapter on biliary atresia), Wilson disease by ceruloplasmin and 24-hour urinary copper excretion, cystic fibrosis by sweat chloride, tyrosinemia by urinary succinyl acetone, alpha-1-antitrypsin deficiency by serum alpha-1-antitrypsin and protease inhibitor phenotyping, and autoimmune hepatitis by presence of autoantibodies and hypergammaglobulinemia (18).

In summary, although viral hepatitis can be self-limited, hepatitis B, C, and delta can cause cirrhosis, death, and liver cancer. Despite the nature of these infections, excellent vaccines can prevent the most common one, hepatitis B. In fact, the hepatitis B vaccine is unique in that it is the only vaccine that can prevent cancer. With the advent of new technologies and gene therapies on the horizon, the outlook for liver disease is favorable.

Questions

1. Why are aminotransferases, alkaline phosphatase, and GGT not considered liver function tests? What is the most useful test for liver function?
2. True/False: Most infants and young children with hepatitis A present with jaundice.
3. A family is planning a vacation in China that is known to have a high rate of hepatitis A. How would you give preexposure prophylaxis to this family who has a 15 month old and a 5 year old child?
4. A labor and delivery nurse informs you that a term infant was just born whose mother is HBsAg negative and anti-HBs positive. How would you approach this infant for prophylaxis?
5. A 1600 gm infant is born to a mother who is HBsAg positive, anti-HBc positive, and anti-HBs negative. The NICU nurse is asking what your order is for this patient. Out of these three HepB tests, which one is the most useful in your decision making process.
6. Name three organ systems involved in Wilson disease and its manifestations.
7. What element is implicated in Wilson disease?
8. What organ systems are involved in alpha-1-antitrypsin deficiency and what are their manifestations?

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Answers to questions

1. These enzymes are found within the hepatocyte, and therefore are indicative of hepatocellular damage, and not actual function of the liver. The most useful test for liver function is prothrombin time.
2. False. They are usually anicteric.
3. The 15 month old should receive immunoglobulin (too young to receive Hep A vaccine). The 5 year old can receive the Hep A vaccine since she is over 2 years of age. The vaccine is given as two doses 6 months apart.
4. The mother is actually immune to hepatitis B, perhaps from receiving hepatitis B vaccinations in the past or from a previous exposure to hepatitis B. She does not have infection, she is not contagious and in fact, she is immune. This infant does not need HBIG prophylaxis, but should be vaccinated against hepatitis B in the usual fashion.
5. The mother has a positive HBsAg, which means that she is contagious. Therefore, this infant needs HBIG and hepatitis B vaccine prior to 12 hours of age. Because this premie is less than 2 kg, a 3-dose vaccine schedule should be instituted after this infant is over 2 kg, and not counting the initial dose because he was less than 2 kg. After completion of the 3-dose schedule, he should be tested serologically for anti-HBs and HBsAg 1-3 months after completion of the series. If his anti-HBs (<10 mIU/ml) is low and HBsAg is negative, then he should receive 3 additional doses of vaccine at a 0, 1, and 6-month schedule, with anti-HBs testing done 1 month later to determine immunity. The mother's status could be consistent with acute hepatitis B, chronic hepatitis B, or a hepatitis B carrier state. The most important serologic test out of the three listed is the HBsAg, since this test tells us whether the mother is contagious and the newborn requires HBIG prophylaxis.
6. Brain (or nervous system), liver, and eye. Manifestations are neuropsychiatric symptoms, hepatitis, and Kayser-Fleischer rings.
7. Copper.
8. Lung and liver. The pulmonary manifestation is emphysema and hepatic manifestations include prolonged jaundice in infants, neonatal hepatitis syndrome, mild elevations of aminotransferases in toddlers, portal hypertension and severe liver dysfunction in older children, and chronic hepatitis, cryptogenic cirrhosis, and hepatocellular carcinoma in adults.

Chapter IX.6. Gastroesophageal Reflux
Ken Nagamori, MD

A one month old male is brought to your office by his first time parents with a complaint of constant irritability and spitting up. The 2.8 kg (6 pounds, 3 ounce) product of an uneventful full term pregnancy and delivery, he was discharged on the second day of life. He always seems to be hungry, and since his mother is certain that she is not producing enough milk, she has been following the breast feedings with formula for the last 2 weeks. He currently will feed at the breast for 10 minutes, then consume another 4 ounces by bottle. When left with his grandparents, he will finish an entire 8 ounce bottle in 5-10 minutes and they report he will cry if they try to cut him off at the recommended 4-5 ounces. The vomiting generally occurs immediately after feedings. It is not forceful, nor is it blood or bile-tinged. He fills 10 diapers with urine daily, and lately he has been having watery stools, which have further worried his grandparents. Despite all this, he weighed 3.5 kg (7 pounds, 11 ounces) at the two week checkup and he now weighs 4.3 kg (9 pounds, 8 ounces).

Exam: VS are unremarkable. His physical examination is notable only for fussiness when laid supine on the table, with resolution when held upright or in the prone position. You witness effortless regurgitation of 2-5 ml of curdled formula every few minutes during the history and exam since his parents "topped him off" with formula in your waiting room before the appointment as he was beginning to fuss.

Gastroesophageal (GE) reflux is defined by the North American Society for Pediatric Gastroenterology and Nutrition (NASPGN) as the "passage of gastric contents into the esophagus" (1). This is a normal physiologic process including regurgitation (the generally low pressure passage of gastric contents up to the mouth) as opposed to vomiting (the forceful expulsion of gastric contents via the mouth) as the latter is more often associated with obstruction or other significant abnormal alteration of gastric motility involving reversal of the usual gastric emptying phenomenon. Likewise, it is to be differentiated from rumination, which is the purposeful return of gastric contents to the mouth as a response to behavioral issues, most typically beginning in the second half of the first year of life and occurring in neglected infants and children in part as self-stimulatory behavior or as a means of getting attention from an otherwise markedly non-interactive (and usually clinically depressed) caretaker.

GE reflux occurs at all ages, and its consideration is best divided between infantile reflux and reflux in the older toddler/child, as the presentations will differ due to responses available due to developmental stage. It can be a chronic and a recurrent problem.

In infants, the more typical presentation is as above, which the NASPGN label "the happy spitter" (1) who freely regurgitates, but more commonly than not, has no sign of respiratory compromise. With the relatively low acid secretory capability and the constant feeding of early infancy, there is less tendency to irritability suggestive of dyspepsia, though many (like the child in the example) will show some sign, and some will become markedly colicky. The attribution of the colicky behavior to reflux is supported by an increase in fussiness in positions where reflux would be promoted; such as supine or slumped in a mal-positioned baby seat, or at times when reflux can be expected; such as following an overfeeding as in our example.

In toddlers and older children, overt regurgitation is less common as they spend more time upright and typically will have learned eating behaviors favoring solids and minimizing liquids which further help retain most of the feedings in the stomach. The retention is not complete, however, and they more typically present with symptoms or signs suggestive of distal esophageal irritation. Aside from complaints of epigastric pain (in the pre-verbal toddler often indicated as holding the epigastrium or refusing to eat further), they can include drooling (caused by reflex hypersalivation triggered by the acid sensors of the distal esophagus acting via the brainstem on the salivary glands), or pronounced eructation (i.e., belching, representing regurgitation of air co-swallowed with the saliva). The latter two are manifestations of the esophageal protective mechanisms, and can be seen in early infancy presentations, just as many toddlers will still regurgitate freely. In the older child and adolescent, hypersalivation is more commonly manifest as a sleeping behavior (as not all the saliva produced while recumbent is swallowed) and often is accompanied by sleep in specific positions of comfort, the most common of which are prone and left decubitus as these offer some positional advantage to mitigate reflux. These options are not available to the infant (particularly in the face of the American Academy of Pediatrics' "Back to Sleep" campaign against SIDS), often resulting in worsening colicky behavior, as noted in our example.

Occasional patients will present with respiratory symptoms as their primary complaint with reflux laryngitis and the contribution of microaspiration of either regurgitated acid or oral secretions (from the hypersalivation) in the exacerbation of chronic asthma is gaining increasing recognition. Though more common as a presenting complaint among older children, it will occur in younger children as well, but is not the more common presentation for any age. A more worrisome presentation is frank aspiration or choking, resulting in pneumonia for the former and symptoms ranging from gagging and sleep interruption to apparent life threatening events (ALTE) for the latter. These more serious conditions require full regurgitation, and are also far less common than the non-respiratory symptoms which require reflux only part-way up the esophagus. The NASPGN have acquiesced to the AAP in dissuading prone sleeping position before 12 months of age, though proning may be used while "awake, particularly in the postprandial period" (1).

GE reflux, and more specifically secondary esophageal irritation (if not frank esophagitis), can result in voluntary reduction in intake in all ages, resulting in classic failure to thrive or frank weight loss. It can result in overt feeding refusal, though it more commonly is manifested as a selective intake, avoiding items which cause pain including acidic and spicy foods, and surprisingly commonly, items with adverse effect on the distal esophagus, including caffeine and chocolate if the examiner questions specifically.

GE reflux must be differentiated from vomiting, as the latter hints at obstruction, and can also arise from metabolic processes (urea cycle defects and Reye syndrome) as well as disease in other organ systems (increased intracranial pressure, pancreatitis, urinary tract infection, or distention of any hollow viscus such as the gallbladder or renal pelvis/ureters). It should also be differentiated from extra-abdominal causes such as post-tussive vomiting, or altered motility due to allergic enteritis or eosinophilic gastroenteritis. In the case above, a one month old with projectile vomiting would suggest pyloric stenosis, but in our case the vomitus is not forceful and has been present from the neonatal period. Projectile vomiting requires an intact lower esophageal sphincter (LES) function to develop adequate intragastric pressure. Since GE reflux is common at this age (>50%), projectile vomiting may not be present in infants with coexisting pyloric stenosis with GE reflux, which may delay the diagnosis of pyloric stenosis.

Three mechanisms produce the majority of GE reflux: 1) Chronically decreased lower esophageal sphincter tone is most common at all ages and can be expected to improve over the first year of life. It is characterized by symptoms which occur more commonly immediately after feedings and further reflect effects of posture or intra-abdominal pressure. 2) Delayed gastric emptying is common among adults due to progressive gastroparesis, particularly with diabetes mellitus, but is less common in children. Characteristically it will produce symptoms which continue for hours after feedings, reflecting the persistently full stomach. 3) Inappropriate LES relaxation is

least common of the three, and typically produces more irregular timing of the symptoms, which tend to be more fleeting as the esophageal protective mechanisms are typically more effective in these youngsters than with the other two.

The diagnosis of GE reflux is typically made by a detailed history and physical examination alone. Regurgitation reliably reported or observed with appropriate adjunct symptoms and signs is suggestive of uncomplicated GE reflux. A careful elucidation of a consistent constellation of symptoms can suggest reflux which is not visible (which is also sufficient to trigger the first lines of intervention). It is in situations where significant secondary disease is present (such as recurrent aspiration, stridor suggesting laryngeal irritation, or failure to thrive with or without frank feeding refusal), that subspecialist assistance should be sought at an early stage, even if overt regurgitation makes the diagnosis fairly certain. Efforts should be made to exclude the other items in the differential diagnosis above, but many can be excluded on the basis of a good history and physical examination of the relevant organ systems.

Radiographic studies are not part of the usual initial workup since the absence of reflux on a short radiographic study cannot rule out GE reflux, and the manipulation inherent in the exam can itself trigger regurgitation. The main utility of the upper gastrointestinal contrast study is to search for structural anomalies such as malrotation as well as the much rarer webs and secondary strictures. These are often accompanied by signs of obstruction (though bilious vomiting may be absent if the obstruction is proximal to the mid-duodenum). The exception is the younger patient with signs of tracheomalacia, as the rare vascular ring, trapping both the esophagus and trachea in its grasp during in utero growth, deserves early intervention. Another exception is pyloric stenosis, for which ultrasound provides less invasive evaluation, permitting earlier access to surgery.

The radionuclide gastric emptying study, likewise is not commonly part of an initial workup, as its prime utility is in assessing delayed gastric emptying. Unfortunately, age appropriate standards are not well established, prompting the use of this test in the more severe cases where surgery is already being contemplated (typically fundoplication). Scintigraphic imaging during the hour-long study can also identify reflux visually (but again cannot rule it out due to the short duration of the study) and 24 hour delayed imaging is cited as being of utility in searching for evidence of aspiration.

pH probes offer a means of assessing the frequency and duration of acid reflux, and with the double-sensor probes, the differentiation between regurgitation and reflux only part-way up the esophagus can be made. Twenty-four hour studies are more reliable than those of shorter duration, since reflux varies with activity and sleep state. Their prime utility is in the patient with symptoms which are clear and disruptive who does not have a clear association with visible regurgitation. The classic example is the infant with repeated ALTEs who is found with curdled feedings. The main issue in such patients in establishing causality is determining whether the reflux came first, then the obstruction, then the apnea. It is more common that the apnea came first, then the agonal relaxation of the LES and regurgitation. In such situations, simultaneous multichannel recordings are essential, since the transition from one stage to the next may be only seconds apart, and on such studies many infants with obstructive apneic episodes and known GE reflux have the two occur at completely different times.

Manometric studies have fallen on disfavor, as they do not address the issues of delayed gastric emptying or inappropriate relaxation of the LES.

For the average healthy infant with no threatening complications, the GE reflux can be approached first with basic mechanical measures:

1) Regulate feedings: As in our illustration, overfilling of the stomach is to be discouraged, and in such a patient, I would recommend the bottle feedings be halted if there is ample evidence of sufficiency of breast feedings. This can be reinforced by following the urine output, with most parents being reassured when told that the fluid urinated had to have been absorbed, and the nutrients associated with that fluid can be expected to be absorbed as well. In the bottle-fed infant, the volume can be calculated, but I have found it easier to give the caretakers a means of identifying the volume that would fit in a minimally distended stomach as being roughly a quarter of the abdominal volume as measured between the ribs and the pelvic brim. This forestalls repeated questions of "how much can we feed now?" as the child grows. The feedings also need to be regularly spaced, to avoid overfilling with too closely spaced feedings. This is less of a problem in the exclusively breast-fed infant, but is not eliminated. For the demanding infant, use of suitable pacification (particularly a parental digit) can be helpful. The feedings also need to be evenly paced, to allow enough time for the infant to feel full and cut off the feeding before overfilling occurs. With the bottle-fed infant, thickening of the feedings is possible; in exclusive breast-feeding, the parental digit will again have to be used.

2) Positioning: Maximizing the vertical distance between the mouth (or more particularly the larynx) and the stomach helps minimize reflux and secondary esophageal irritation (i.e., colic). The literature does support prone positioning in this regard, but the cautions noted above regarding SIDS apply. It is worth mentioning to parents, however that infants choose their own sleeping positions once they are able to roll from supine to prone around 4 months of age to avoid many sleepless nights repeatedly rolling their infant back into the supine position only to flip back as soon as he or she is free to do so. Decubitus positioning provides some relief, as can positioning in a recliner (as long as the angle chosen does not cause slumping). There will be times when carrying the infant upright may offer the only relief (particularly after overfeeding).

3) Thickening the feedings may be a consideration in the formula fed infant, and is far less practical in the breast-fed one. In many cases the greater utility of the thickening is in slowing the feeding rate than in any retention within the stomach. Rice cereal is preferred over the recently introduced formulas that thicken when exposed to acid (recall many young infants may not produce much acid). Typical recipes call for one-half to one tablespoon of rice cereal per ounce of formula, which also adds substantially to the overall caloric intake. Thickening to encourage retention in the stomach is of most use in those with evidence of chronic low LES tone (spitting which occurs predominantly shortly after the meal) and can be less than useful in those who have delayed gastric emptying (with spitting which continues for hours after a meal) as it may cause further delay in emptying. In such infants who are formula fed, one of the cheaper partially hydrolyzed formulas may provide the better option, as fluids empty from the stomach faster than curd. In that respect, breast feeding, with its thinner curd, tends to empty faster than most formulas.

In older toddlers and children:

1) Regulate the feedings: Many with secondary esophageal irritation (if not frank esophagitis) will tend to complain of nausea and anorexia in the morning, and skip or minimize breakfast intake. They may or may not eat much lunch, particularly if the school is providing a spicy menu. They often eat more of their daily caloric intake throughout the afternoon and evening. Redistributing the intake to be more evenly spaced during the day will result in less nocturnal acid reflux and is of most utility in those complaining of symptoms after supper or nocturnal waking or morning nausea. Avoidance of after supper snacking can also help.

2) Positioning is less of a problem once infants pass 6 months of age and can choose to be upright. For older children, the option of elevation of the head of the bed for sleep is often declined as more seem to prefer prone positioning.

3) Avoid agents prone to adversely altering LES tone and functioning such as caffeine and nicotine.

In all age groups, a therapeutic trial to address acid can be of significant diagnostic utility. My personal preference is to use antacids, since this provides immediate pain relief (good reinforcement). Typical therapeutic courses with histamine-2 receptor blockers or proton pump inhibitors run 6-8 weeks with only partial resolution. In infants, the aluminum containing antacids should be avoided since aluminum absorption may cause osteodystrophy. A typical therapeutic trial yields suggestive results within 2 weeks, and can be helpful in determining whether an atypical (but non-threatening) symptom is acid-related.

Beyond these basic steps, the evaluation and therapy diverge based on the dominant symptoms. If delayed gastric emptying is the issue, therapy centers on properistaltic agents and may include a more thorough evaluation of structure and gastric emptying. If pain or other inflammatory signs are dominant (i.e., reflux laryngitis), acid secretion suppression or blockade are the mainstay, and endoscopy (with biopsy) offers the best diagnostic discrimination. These measures typically prompt subspecialist assistance.

Infantile reflux typically presents with overt regurgitation and dyspepsia (colic). These can be expected to improve markedly over the first year of life with the transition to a diet based more on solids than liquids and attainment of a more upright posture. Conversely, GE reflux in the older child tends to present as chronic or recurrent pain, with only secondary signs or symptoms of reflux and no overt regurgitation. It represents a chronic problem, the symptoms of which may run life-long, and if mechanical measures and intermittent acid neutralization do not provide adequate symptomatic relief, long-term medical therapy may be warranted. In either case, in the absence of life-threatening complications, surgical options are not a routine consideration, and generally are considered only in the face of failure of extended and aggressive medical management of significant levels of disease.

Questions

1. True/False: Gastroesophageal Reflux is a rare phenomenon in childhood.

2. For the vomiting infant:
   a. The parents can be reassured it is a process the child will outgrow as they get older.
   b. Thickening the feedings sometimes works.
   c. Proper positioning may be helpful.
   d. Deserves further evaluation.

3. A one month old second born female presents with worsening of her GE reflux. The regurgitation remains effortless, but is increasing in volume and seems more prominent an hour or so after meals. She has been more demanding of feedings and has had fewer wet diapers over the last few days and is losing weight. Her parents have felt "something moving" in her stomach in the hour after feedings over the last week. What is happening?

4. True/False: A 4 year old with complaints of abdominal pain that disrupt school attendance warrants a two week trial of a proton pump inhibitor.

5. True/False: A diagnosis of pain due to gastroesophageal reflux is likely to lead to a lifetime of expensive medication.

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Answers to questions

1. False. Though most episodes are asymptomatic, reflux is a routine physiologic phenomenon in everyone, at every age. It is gastroesophageal reflux DISEASE that is uncommon in most of childhood.

2. d. Remember regurgitation is effortless, vomiting is forceful and is atypical for uncomplicated GE reflux. It can indicate obstruction or metabolic derangement, and represents a problem that requires an answer in as short a period of time as possible (even if the answer is a diagnosis of routine gastroenteritis).

3. Consider pyloric stenosis, even if only a few of the classic symptoms and signs are present. Waiting for the diagnosis to become more obvious further delays surgical intervention and increases the risk of complications such as hypochloremic alkalosis and dehydration. See differential diagnosis above.

4. This one is arguable, but my personal preference is to start treatment with antacids since it offers a means of immediate relief of any truly peptic pain episode, and younger children are better reinforced by immediacy of the response. Of course a good history and physical should come first to verify the pain does fit a "peptic" pattern, as constipation is more likely at this age.

5. False. The vast majority of uncomplicated pain seems to respond to mechanical measures, avoidance of caffeine, nicotine, and the like, and intermittent antacid use. It is only when the pain episodes remain disruptive more than once weekly that it is generally warranted to proceed to chronic medical therapy, and then only at the minimal doses necessary unless other complications (e.g., Barrett's esophagus) occur.

Chapter IX.7. Gastrointestinal Foreign Bodies

Lu'ukia Ruidas, MD

A 2 year old previously healthy male is brought to the emergency department by his mother with a chief complaint of gagging. The patient was playing alone when his mother found him gagging and coughing. There were no apneic or cyanotic episodes and the child denied any pain. The gagging ceased after a minute and he was breathing normally. Later that evening, he was watching TV with his mother and again had a gagging episode lasting a minute. His past medical history and family history are unremarkable.

Exam: VS T 37, P 110, R 30, BP 95/60, oxygen saturation 98% on room air. He is alert, cooperative, non-toxic, and in no acute distress. The oral cavity is without lesions or erythema. Lung exam reveals clear lung fields and normal breath sounds. The remainder of the exam is unremarkable.

AP and lateral chest radiographs, obtained 3 hours after his mother noted the first episode of gagging, reveals a coin lodged in the proximal esophagus. A gastroenterologist is consulted and the child is taken to the operating room for endoscopic removal of the coin.

Eighty percent of all foreign body ingestions occur among children (1). Children aged 6 months to 3 years are especially prone to foreign body ingestions since they taste and swallow nearly everything while exploring their surroundings (2). In the United States, about 1500 ingestion cases end in death annually (3). Many of these deaths occur in children with preexisting gastrointestinal (GI) abnormalities, such as fistulas, diverticula, webs, or rings, since these abnormalities put them in danger for foreign body impaction and its complications.

While any small object is an ingestion hazard, coins, food, toy parts, disc batteries, paper clips, needles, earrings, bottle caps, and marbles are among the most common objects ingested by the pediatric population. Nearly all objects that reach the stomach will pass spontaneously over a period of 4-7 days (1,4). Three points in the esophagus represent the most narrow regions of the GI tract. These are the cricopharyngeus muscle in the proximal esophagus (where the cricoid ring impinges on the esophagus), the aortic arch crossover in the midesophagus, and the lower esophageal sphincter. The cricoid region is the most common place to find a foreign body. If the foreign body manages to pass into the stomach, it has already passed the three narrow points in the GI tract so it is very likely to pass spontaneously. However it is possible, though unlikely that the foreign body may have difficulty passing through other narrow points such as the pylorus, duodenal sweep, ligament of Treitz, and the ileocecal valve. Therefore, the clinical approach to GI foreign bodies depends on the type of object ingested and its location along the tract. Dividing the GI tract into three distinct areas, the oropharynx and esophagus, stomach, and intestines, aids in organizing the clinical approach to foreign body ingestions.

A child with a foreign body in the oropharynx or esophagus may present with a foreign body sensation in the throat, airway compromise due to impingement of the easily compressed pediatric trachea, drooling, dysphagia, coughing, gagging, vomiting, or throat or chest pain. A foreign body in the stomach or intestines will not usually cause symptoms. If symptoms are present, they commonly result from complications in these areas such as perforation or obstruction. Symptoms include abdominal pain, hematochezia, nausea, vomiting, hematemesis, or fever. Still, up to 40% of patients with foreign bodies are asymptomatic, regardless of location (1).

On physical exam, inspection of the oropharynx may reveal the foreign body, abrasions, blood, or erythema. Physical findings are unusual with esophageal foreign bodies unless there is tracheal compression, in which case stridor or wheezing may be present. Similarly, the examination of a patient with a gastric or intestinal foreign body is unlikely to reveal any specific findings. Signs indicating perforation or obstruction of the lower GI tract should be sought.

Because the symptoms of foreign body ingestion are often nonspecific, the list of differential diagnoses encompasses a wide variety of conditions. These include pharyngitis, esophagitis, reactive airway disease, pneumonia, pneumothorax, gastroenteritis, and appendicitis. Fortunately, there is often a history consistent with foreign body ingestion from the caregiver, who witnessed the ingestion or from the child, who reported the ingestion to a caregiver. Nonetheless, the possibility of foreign body ingestion should always be considered when caring for children.

Radiographic imaging from mouth to anus should be obtained in any child suspected of ingesting a foreign body, as it is often difficult to determine the exact location of the object from the history and physical. If an oropharyngeal foreign body is visualized on the physical exam of a cooperative, stable patient, attempts can be made to remove it with forceps. Otherwise, indirect laryngoscopy, fiberoptic nasopharyngoscopy, or plain films may help localize the object, most commonly a fish or chicken bone. If the object is visualized but attempts to remove it are unsuccessful, arrangements should be made for endoscopic removal. In the case where the object is not visualized by any of these techniques, endoscopic evaluation should, likewise, be obtained (3). Although an endoscopically confirmed object is found in only 17-25% of patients complaining of a foreign body sensation in the throat, endoscopy may reveal esophageal abrasions or mucosal tears that may be causing the sensation (3). Patients with potential airway compromise or evidence of perforation should first receive airway protection and then referred for immediate endoscopy.

Radiopaque objects in the esophagus are consistently visualized on the mouth to anus screening radiographs obtained for suspected foreign body ingestion. The objects will frequently be seen in one of three locations along the length of the esophagus. In the pediatric population 60- 80% of objects get caught at the level of the cricopharyngeus muscle in the proximal esophagus, 10-20% become trapped at the level of the aortic crossover, and 5-20% are found at the level of the lower esophageal sphincter (3). Coins account for the majority of esophageal foreign bodies in children. Radiographically, a coin in the esophagus is seen as a disk in the anteroposterior projection and from the side on lateral films as it is lodged in the easily compressed esophagus, which lies posterior to the trachea. Conversely, a coin in the trachea is seen from the side on anteroposterior films and as a disk on lateral films as its orientation conforms to that of the vocal cords en route to the trachea (however, most coins cannot fit in a pediatric trachea). Although AP films are sufficient to determine whether the coin is in the esophagus or trachea, based on its orientation, lateral films should also be obtained to ascertain whether there is more than one coin lodged in the esophagus, not easily seen in the AP projection. Radiolucent objects in the esophagus, such as plastic, wood, or aluminum can tabs, are difficult to detect on plain films. In this case, CT, contrast radiography or endoscopic examination should be obtained.

Management of an esophageal foreign body depends on the type and location of the object. Any sharp, rigid, or long (>5-6 cm) object should be removed endoscopically since these objects are associated with a high incidence of esophageal and lower GI tract perforation (1,2). Objects in the proximal and mid esophagus should also be removed endoscopically since they usually do not pass spontaneously into the stomach (5). A single blunt object located in the distal esophagus for less than 24 hours in an asymptomatic, otherwise healthy patient may be allowed to pass spontaneously into the stomach if close follow up can be assured. However, if passage is not seen on radiographs obtained 24 hours after ingestion, the object should be removed endoscopically since objects allowed to remain in

the esophagus for more than 24 hours are associated with mucosal inflammation (6). Patients with respiratory difficulties or those showing signs of esophageal perforation should be immediately referred for endoscopy.

Several other removal techniques have been described for blunt esophageal foreign bodies in an asymptomatic or minimally symptomatic patient. The Foley catheter method, done by experienced personnel, involves inserting the deflated catheter orally, past the object. The balloon is then inflated and the catheter is slowly withdrawn, pulling the foreign body ahead of it. The use of glucagon to relax the smooth muscle of the lower esophageal sphincter and allow passage of the object into the stomach has also been described. Success rates using glucagon in children range from 30-50% (2). Frequent side effects of glucagon are nausea and vomiting. While these techniques may be cost effective, compared to endoscopy, they do not offer airway protection or allow visual evaluation of the GI tract (1).

Asymptomatic patients with foreign bodies in the stomach may be observed for spontaneous passage of the object. If movement from the stomach is not detected on follow up radiographs in 7 days or if the patient becomes symptomatic, referral for endoscopic removal is required (4). Sharp gastric or duodenal foreign bodies should be removed by endoscopy immediately since 15-35% of sharp objects will perforate the lower GI tract (3). As mentioned previously, long objects should also be removed endoscopically since these might not be able to navigate through the duodenal sweep.

Once the foreign body reaches the intestines, it will likely pass through the rest of the GI tract successfully. If the object remains in any region of the lower GI tract for more than 7 days or if the patient develops signs or symptoms of perforation or obstruction, the foreign body should be removed surgically (2). If a sharp object passes beyond the pylorus, endoscopic removal is more difficult so the patient should be followed with daily radiographs and observed for signs of perforation and bleeding. If complications do develop, the patient should be referred for surgical removal of the object. By the time a sharp object reaches the colon, it becomes surrounded by fecal material and is able to pass though the rest of the lower GI tract safely.

Complications of foreign body ingestion can occur throughout the GI tract. These include airway compromise, abrasions, perforation with resultant abscess formation, obstruction, ulceration, fistula formation, or vascular injuries. With the advent of endoscopy, more foreign bodies are successfully removed resulting in less complications.

Disk or button batteries are small, coin-shaped batteries used in hearing aids, watches, and calculators. Prior to 1982, only a few cases of disk battery ingestion were described (4). As the use of these small electronic gadgets have increased, the problem of disk battery ingestion has become more common. Seventy percent of disk battery ingestions occur in children aged 6 to 12 years (1). The danger of disk batteries is that they contain mercury, silver, zinc, manganese, cadmium, lithium, sulfur oxide, copper, and sodium or potassium hydroxide. If the battery becomes lodged in the GI tract it may cause pressure necrosis, low-voltage burns, or ulceration due to liquefaction necrosis stimulated by leakage of the battery's alkaline solution (2). As little as one hour of contact between the battery and esophageal mucosa may result in injury (4). Because of the damage that can occur in the esophagus, endoscopic removal should be done immediately after localization by radiographic imaging. On the anteroposterior projection, disk batteries can be distinguished from coins by the double-density shadow of its bilaminar structure (4).

If the battery is located in the stomach, there is a 90% chance that it will pass through the GI tract spontaneously (3). As the battery is allowed to pass, patients should be monitored for signs of perforation or bleeding. If these complications become evident or if the battery has not moved beyond the stomach in 3-4 days, endoscopic removal should be performed. Endoscopy will also allow for visualization of the upper GI tract for evidence of ulceration or necrosis caused by the battery. Batteries that pass into the intestine are generally eliminated without consequence. Though there may be concern about mercury toxicity should the contents of the battery leak out into the GI tract, mercury oxide, is not readily absorbed by the GI tract (1). Therefore, the risk of toxicity is low.

Bezoars are accumulations of exogenous material in the stomach and small intestine. They are classified according to their composition. Trichobezoars are accumulations of hair, often the patient's own. Ninety percent of patients with trichobezoars are females aged 10-19 years with trichotillomania and trichophagia (4). Phytobezoars are composed of plant and vegetable matter. Persimmons, celery, pumpkin, grapes, leeks, and grass have all been known to form phytobezoars if they are ingested in great amounts. Lactobezoars are formed by milk components. Though the reasoning is not clear, the majority of lactobezoars are found in premature, low birth weight infants (7). Factors associated with lactobezoar formation may include rapid advancement in feedings, high calcium and protein content of specialized formulas, or the unique gastric physiology of premature infants. Antacid bezoars are accretions of dehydrated antacids, commonly seen in patients with poor gastric motility or patients receiving high dose antacid therapy.

Bezoars, regardless of composition, often present with symptoms of abdominal pain, anorexia, nausea, and vomiting. The physical exam may reveal abdominal distention or a palpable abdominal mass. Bezoars may be visible on plain films but computed tomography with contrast is the imaging technique of choice since it allows for estimation of the size of the bezoar, which often directs management. Endoscopy allows direct visualization of the bezoar and also provides information on its content. Most trichobezoars are managed surgically. Small trichobezoars may be removed in fragments by endoscopy. However, the density of the bezoars often presents a challenge. Phytobezoars are frequently dissolved using a clear liquid lavage and metoclopramide or endoscopic fragmentation. Otherwise, surgical removal is required. Feeding withdrawal for 48 hours with maintenance IV hydration is usually all that is required for resolution of lactobezoars.

Questions

1. At what three areas of the esophagus are foreign bodies commonly located?
2. If a coin is seen as a disk on the anteroposterior film, is it in the esophagus or trachea?
3. True/False: A sharp object in the distal esophagus may be observed for 7 days if the patient is asymptomatic.
4. True/False: There is a high risk for mercury toxicity if the contents of a disk battery leak into the GI tract.
5. What are phytobezoars?
6. If an 12 month old swallows a penny, is there any possibility that it is in the trachea?
7. What accounts for the increased incidence of ingested disc batteries?

Related x-rays

Esophageal coin case: Yamamoto LG. Hemoptysis Identifies An Esophageal Coin. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1995, volume 2, case 1. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v2c01.html

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Answers to questions

1. The level of the cricopharyngeus muscle in the proximal esophagus, the aortic arch crossover in the midesophagus, and the lower esophageal sphincter.
2. The esophagus because of its orientation.
3. False. A sharp object in the esophagus should be endoscopically removed immediately to prevent perforation.
4. False. The mercuric oxide in disk batteries is not readily absorbed by the GI tract.
5. Accumulations of plant and vegetable matter.
6. A penny cannot fit in an infant's trachea.
7. More gadgets which use disc batteries increases the likelihood that these batteries will be left around the house for young children to put into their mouths.

Chapter IX.8. Constipation
Ken Nagamori, MD

Case #1: At her one month well child visit, worried parents ask about their child's protuberant abdomen. She had been breast-feeding well during the first week, but her intake has been declining and she has begun spitting up. Physical examination finds lethargy, pallor with diaphoresis, tachycardia, distended loops of bowel, and rectal examination finds a narrow anus, and further insertion gives the impression of putting on a glove two sizes too small. The narrow canal extends for two centimeters, then widens into a pool of loose stool. When the examining digit is withdrawn, it is followed by a sudden spurt of particularly foul-smelling stool laden with mucus and streaked with blood, accompanied by a moderate amount of flatus. Questioning the parents identifies the failure to pass stool or flatus without stimulation with a rectal thermometer, having received instruction to do so from her aunt who is a nurse.

An abdominal series is obtained which demonstrates dilated bowel loops and a pattern resembling an acute bowel obstruction. Hirschsprung's disease with acute enterocolitis is suspected.

Constipation is a commonly used term, but its definition is somewhat ambiguous. It could refer to conditions such as: a) the stools are hard, b) the stool is difficult or painful to pass, 3) no stools for a period of time, 4) a bloated feeling, 5) painful cramps associated with a segment of stool that is not moving well, 6) a chronic condition in which a patient's stooling frequency is less than average. All of these definitions are used in medical and/or everyday communication, but it is preferable to use specific terms to describe the symptoms of the patient. The specific findings and their clinical significance will be described in this chapter.

Enterocolitis (as seen in case #1) is the extreme sequel of fecal retention, and is almost unique to Hirschsprung's disease, itself a uniquely pediatric version of the broader definition of chronic constipation: "a delay or difficulty in defecation, present for two or more weeks, sufficient to cause significant distress to the patient" adopted by the guidelines of the North American Society for Pediatric Gastroenterology and Nutrition (NASPGN) (1). The subject is best broken into two broad categories: infants and children.

Infantile constipation: Per the guidelines, this does not include neonatal delays in defecation since the structural anomalies (imperforate anus, cloacal exstrophy, and other perineal anomalies, as well as intestinal atresia, stricture or web, volvulus, duplication, or perforation) and genetic diseases (e.g., meconium ileus of cystic fibrosis) often present in the first few days. Newborns should pass their first meconium stool within 24 hours. Those who don't have a higher risk of GI conditions associated with constipation. However, this criterion should not be relied on in isolation since pathologic conditions will not necessarily present this way. The algorithm proposed by the NASPGN constipation subcommittee emphasizes early suspicion of serious disease, by rapidly sorting out newborns with delayed passage of meconium for rectal biopsy and directing infants with "fever, vomiting, bloody diarrhea, failure to thrive, anal stenosis, tight empty rectum, impaction and distention" (1) to immediate further evaluation, including subspecialty consultation as needed.

The workup begins with a thorough history and physical examination. The above alarm indicators are searched for, as are signs of other structural anomalies. The rectal examination is key, with careful assessment of the anal location, anal neurologic function (the anal wink, which assesses both the sensory afferent and motor efferent pathways), anal structure (looking for distention of the internal anal sphincter), anal tone (looking for spasticity or patulousness), function of the muscles of the pelvic floor (which provide additional help with control of defecation), and rectal diameter and tone (looking for signs of chronic distention even if no stool is present on the day of exam). The anal location should be halfway between the posterior border of the scrotum or posterior fourchette and the tip of the coccyx. Anything outside of the middle third of this region should raise the suspicion for a "perforate imperforate anus" (a structure resembling an

anus is visible externally, but it is not contiguous with the rectum). If benign constipation is found, treatment is stratified based on age and developmental state.

Exclusively breast fed infants are permitted a longer interval between stools if they show no signs of distress or distention and if they are not prone to becoming impacted.

In exclusively formula-fed infants, my favorite strategy is the substitution of a commercially available partially hydrolyzed formula, which may produce suitable loosening of the stools. Malt soup extract (a dehydrated powder derived from an effusion of malted barley used in the brewing industry) has been advocated by the committee, as have corn syrup, lactulose or sorbitol, while the use of mineral oil was cautioned against due to the risk of aspiration posed by the frequency of gastroesophageal reflux and swallowing incoordination in this age group.

Impaction is most commonly dislodged by glycerin (non-stimulant) suppositories for which the commercially pre-softened versions sold in soft plastic applicators (glycerin gel) have been my personal favorite, as they provide more immediate relief (the traditional refrigerated suppositories require a wait while they melt in situ). Stimulant enemas are to be avoided in young infants.

Older infants who are of an age where pureed foods would be appropriate should have the fiber content of their diet optimized (i.e., push fruits and vegetables and reduce the other starches). Another personal favorite in the older formula fed infant is the use of undiluted apple juice (not apple drink) for its sorbitol content, titrating the amount administered to the stool texture while making certain that formula intake remains adequate. Pear and prune juice can also be used as they are high in sorbitol, but the cost of the former and the TASTE of the latter are often limiting factors.

Case #2: This 6 year old male presents with fecal soiling on a daily basis, which began in late October. He claims he "can't tell when" he is about to soil. His parents report multiple bouts daily of fecal urgency where he rushes to the toilet, only to pass small amounts of diarrheal stool. His toilet sitting behavior is peculiar in that he sits far back on the toilet seat with his knees extended and his toes pointed, straining at defecation. Once or twice weekly he will pass a very large caliber formed stool, which has on occasion plugged the plumbing. This pattern was not thought to be a problem by his parents as it began shortly after they began potty training him at two years old so that he could enter preschool earlier than rest of the neighborhood children. The dietary history finds that he eats the school breakfast and lunch, and will often not touch his vegetables at supper. Closer questioning indicates he does not pick fruit or vegetables from the salad bar at school, and the school typically offers only sweet buns or a burrito for breakfast. Physical examination finds a midline mass in the lower abdomen, with a rectal examination that shows a normally placed anus with an intact anal wink and a perineum coated with stool. The anus is shortened with the internal anal sphincter dilated by a massive boule (little football) of formed stool. You are unable to accurately assess the diameter of the rectum as the stool appears to fill the pelvic bowl. The stool tests negative for occult blood.

Unlike the child with Hirschsprung's disease in the first illustration, the retention of stool in the older child who does not have a structural or neurogenic anomaly (as seen in case #2) will NOT cause secondary inflammation and enterocolitis, regardless of the duration of the problem. This lack of inflammation is an important differentiating factor that permits immediate identification of the older child with chronic constipation. The primary cause is voluntary fecal withholding, usually due to fear of pain on defecation, giving rise to the term "Psychogenic Constipation". The often accompanying overflow diarrhea or involuntary soiling arising from passage of looser chyme above and around the impaction is termed Encopresis in verbal analogy to enuresis. In simpler terms, the child has a football shaped mass of hard stool in the rectum which reduces the sphincter's ability to hold in liquified stool (chyme) coming from above, which results in soiling. The withholding behavior most often arises from a pattern of passage of large caliber stool as was the case with our illustration, but it can arise in response to a single traumatic event, such as a particularly large stool resulting in a traumatic fissure, a too-rapid transition from diarrhea with a raw perineum to fully formed stools, perianal cellulitis (more properly erysipelas, an intensely painful superficial infection of the anus and surrounding structures with Group A streptococcus identifiable by culture of the affected area), or least frequently but most insidious: overt trauma of physical or sexual abuse.

As in infantile constipation, the history and physical exam are key. The above historical markers are useful in establishing an understanding of the process by the patient and his or her caregivers. Dietary issues must also be explored, as well as the pattern of toileting (it is amazing how little time and opportunity school age children seem to have for sitting on the toilet, with some schools having policies of allowing only two minutes per bathroom break).

The issues on the physical examination of the older child are the same as those of the infant, particularly those regarding the rectal examination. Indicators of failure to thrive are more important beyond the first year, since celiac disease and cystic fibrosis occasionally present with constipation instead of diarrhea, and Crohn's disease can leave the rectum fully capable of extracting fluid from the reduced flow of chyme arising from the reduced appetite, if the inflammation is confined to the small bowel or proximal colon. Hypothyroidism is a particularly rare (but often cited) cause of constipation. A particular caution regarding Hirschsprung's disease bears noting as a significant fraction of the cases present beyond the second year of life in children who require stimulation to trigger defecation: repeated suppositories and enemas will often dilate the spastic segment making it impossible by digital examination alone to identify what should otherwise have been a microcolon. If suspicion is high (inability to spontaneously pass flatus or a strict requirement of stimulation to pass stool which when triggered tends to be foul, loose, and voluminous), an unprepped barium radiographic colon examination is indicated. This study should specifically look for a transition zone, to and fro peristalsis in the unobstructed segments, or uniform mixing of the contrast material throughout the colon (rather than concentration of the remaining barium in the rectum) on the 24 hour delayed film (hence the stipulation for barium rather than water soluble contrast which would tend to be absorbed by the next morning). If the radiographic study is equivocal, anorectal manometry may be of benefit. If either are indicative of Hirschsprung's disease, the diagnosis is confirmed by biopsy of the rectum deep enough to include the myenteric plexuses, as their absence indicates the disease.

If simple constipation without impaction or soiling is identified, therapy begins with education regarding the need for a more regular defecation pattern to prevent progression of the problem.

Dietary intervention is advocated, emphasizing fiber and fluid in accordance with proper nutritional guidelines. Here I find a concrete set of recommendations is most helpful in facilitating compliance, and I have abridged the USDA's food pyramid (2) to a set goal of 6 servings of fruit or vegetables daily with a like number of servings of fluid, which is even further simplifiable to 2 servings of fruit or veggies at each meal which is easily understood by preschool AND adolescent patients.

More importantly, the need for regular toileting in the already potty-trained is emphasized, and I ask that they sit on the commode twice daily after meals to take advantage of the gastrocolic reflex to promote more regular rectal emptying. As in our illustration above, there must be an immediately preceding meal for the process to be most effective, and I have found that eating two fruits before toileting to

be helpful. Suppers eaten out should be followed by a trip to the restaurant toilet to avoid missing the increased post-prandial peristaltic activity. A five minute time limit is set for commode sitting to avoid any sense of a punitive nature to the requirement and in some cases I will advocate using a kitchen timer in a "beat the clock" game if appropriate for the patient's personality.

Encopresis on the other hand is an indicator of repeated impaction, and usually is accompanied by enough dilatation as to render the rectal musculature patulous. Here again, education is key, and to simplify the biophysics (the wall tension is proportional to the fourth power function of the bowel lumen diameter), a quick analogy to a balloon that has been repeatedly inflated to the point of flaccidity is readily within the experience of most 4 or 5 year olds. Likewise an analogy to repeatedly compacting the trash over a 3-4 day period rather than dumping it daily will usually trap a kindergartner into admitting such behavior is likely to lead to a heavier, harder and bigger trash bag (and stool). Most importantly, education and discussion is important which should center on the cycle of pain at defecation leading to withholding which results in larger, firmer stools which in turn leads to more pain at defecation, perpetuating the cycle. This helps create understanding in the patient and the parent as to the origin of the process and its ultimate eradication. A thorough discussion of the mechanics of impaction and overflow passage of the as-yet unformed stool around the obstruction helps explain why distention of the rectum and internal anal sphincter and distortion of the levator structures of the pelvic floor result in inadvertent passage of loose stool whenever voluntary control of the external anal sphincter is relaxed. A thorough understanding is important in defusing the animosity that often arises between the patient and caregivers (parents, school, babysitters, etc.) over misunderstanding of what causes and perpetuates the soiling.

Treatment in the impacted, encopretic patient starts with disimpaction. High dose mineral oil and polyethylene glycol bowel preparation solutions have demonstrated efficacy and magnesium citrate, lactulose, sorbitol, senna and bisacodyl having been used anecdotally (1). Though the NASPGN subcommittee found that the oral route can be effective, typically this route is messy and more time-consuming. I strongly prefer a series of hypertonic phosphate soda enemas that are administered at 12 hour intervals (3). Typically only 3 are required, but the importance of removal of all formed elements is emphasized to prevent worsening the overflow diarrhea in the face of the fecal softening to follow. Caution is advised in using too much or too many enemas as each leaches a substantial bolus of calcium. In the case of particularly large and firm impaction, pre-softening by application of a mineral oil enema an interval before the stimulant one can be helpful. Saline enemas were also advocated by the committee as safe and effective, but soap suds, tap water and magnesium enemas are discouraged due to toxicity (1).

The next step is fecal softening, the issues being two-fold: produce a stool loose enough to be eliminated by the patulous rectum, AND eliminating any association of pain with defecation. Again, while the committee found lactulose, sorbitol, magnesium hydroxide, magnesium citrate, and mineral oil to be effective (1), I strongly prefer mineral oil (3) starting at 2-3 ml/kg/day but specifically titrating the dose to achieve the desired stool texture which I specify as "pancake batter", which has enough form to be routinely retained by the internal anal sphincter yet which is loose enough to empty out of the rectum with little more force than that of gravity alone whenever the levator structures of the pelvic floor are lowered and the anal sphincters are opened. In most cases, a patient whose rectum is dilated enough to allow soiling will have trouble expelling stool even the texture of toothpaste, which is the softest that can routinely be expected from fiber and fluid alone. A looser stool is needed to start the process, and mineral oil provides the cheapest and least flatulent method of attaining that goal. While the committee also made provisions for short-term addition of laxatives to this regimen (1), I feel anyone whose rectum is patulous enough to require such additional assistance, should have subspecialist evaluation, as this is by far the exception rather than the rule.

The third step is effective toileting: the already potty-trained patient should be seated on the commode with good foot support (to obviate any tendency to use the musculature of the buttocks and legs to assist in further withholding activity) on the commode twice daily after meals under the same guidelines and for the same reasons as outlined in the simple constipation as above. The sitting is made "non-negotiable" simply to ensure its application as it will become the most enduring and important part of the regimen as the weaning process progresses. Those who are not yet potty-trained are excused from formal sitting but are encouraged to crouch in diapers after meals in an analogous fashion.

Once a better than daily bowel habit is established and withholding is clearly extinguished, weaning off the mineral oil can begin. It is taken VERY slowly, in part to avoid recurrence of pain and resumption of withholding, but more to allow time for the patulous rectum to regain motor tone. I illustrate the importance of this to the patient and family by referring back to the balloon illustration, pointing out the difference between inanimate latex and living muscle, which can regain tone and function. I specifically warn that the process will take months to improve, and that prolonged use of mineral oil has been proven benign (4). This helps improve adherence to the long-term nature of the measures involved, and weaning typically occurs at monthly intervals, and then ONLY if the rectum is indeed shrinking in diameter (and improving in function) and if the withholding remains extinguished. Failure with either issue should result in either maintenance at the current step or return to the next higher one.

Adherence to the mechanical measures involved typically results in an immediate return to continence with the completion of disimpaction, as the nondistended internal anal sphincter is able to retain the loose stool. Continued adherence to the slow weaning typically results in return to long term function (and confidence) through the months of steady increase in stool texture. Permanent adherence to a daily defecation pattern results in long-term avoidance of reimpaction, and is the ultimate goal of the process. Each step along the way involves the physician acting as coach, cajoling and encouraging patients and caregivers, solving problems in techniques, and refereeing any residual conflicts. It must be kept in mind that control in this issue lies with the patient. There is nothing we can (or should) do that will force regular toileting, and there are times when I have to call a "time out" from the process to enable the patient to proceed on his or her merry way until THEY are ready to work on the problem. I often remind parents that the only thing one will die of with routine encopresis is embarrassment, remembering that children are often beaten to death by caregivers for soiling behavior. As can be seen above, the initial visit to address the issue of encopresis can be particularly time-consuming, not with regard to the history or physical examination, but because of the need to impart the understanding of the process of the disease that will encourage an apprehensive child to undertake the measures needed to clear it. The hour rapidly fills with illustrations and instruction, and does not readily fit into a routine sick-child office visit. Time must be set aside for proper handling of the process, and I know most consultations for encopresis arise from the inability to carve out such time in the primary care practice setting.

Questions

1. The nurse points out a two day old healthy term infant who is otherwise ready for discharge who still has not passed meconium. Your next step is:
   a. Order a suppository prior to discharge.
   b. Careful physical examination, including digital rectal examination.
   c. Give a normal saline enema to prep for a barium enema.
   d. Call radiologist to discuss an unprepped barium enema
   e. Rectal biopsy.

2. The exam of a 3 year old with recurrent impaction is normal except for the impaction and the absence of an anal wink. Which of the following are true.
   a. An anal wink is not commonly found in this age group.
   b. The anus may be so traumatized by the impaction that the wink cannot be reliably elicited.
   c. There may be a neurogenic component to the problem in addition to the psychogenic one.

3. Your examination of a chronically soiling 13 year old female finds a normal sized rectum containing soft stool. Is this routine encopresis?

4. A 6 month old infant has been getting suppositories and enemas every 3-4 days because she does not otherwise defecate. The stools were passed without apparent trouble on breast feeding. Rectal examination finds a normal sized rectum as far as you can reach. Does this rule out Hirschsprung's disease?

5. The barium enema performed yesterday was read as normal, but the remaining barium did not pass overnight. You obtain a followup film this morning, and find dilute barium evenly distributed from the cecum to the rectum. What is the likely diagnosis and why?

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2. www.nal.usda.gov/fnic/Fpyr/pyramid.html
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Answers to questions

1. Answer d is correct, and the radiologist will appreciate the warning as to why the exam is being requested without prior bowel cleanout (which may otherwise be performed as part of the radiology routine, rendering the same end result as answer c). Answer a will not only miss the diagnosis but may also render diagnosis more difficult later if the pattern is set for stimulation for defecation. Answer b may give the diagnosis if a microcolon can be identified on exam, but can make interpretation of a barium enema difficult. Answer c is wrong for the same reasons as a and b. Answer e is doing too much too soon.

2. Correct answers are both b and c. Anal winks can be expected at any age unless the anus has indeed been badly traumatized. Its absence usually indicates a neurogenic component, and the examiner is prompted to carefully assess the tone of the sphincter and retrospectively look for other signs of aberrant function of the longer neuron sensory and motor tracts or signs of sacral anomalies. If the issue is still in doubt, it can be deferred by one visit. The process can still be addressed by full fecal softening and re-establishment of regular bowel habits since the therapies diverge at a later stage where a timing suppository needs to be added to maintain regular defecation as the weaning progresses and the stool becomes firmer. Full fecal softening is needed initially for both causes to address the flaccidity of the rectum.

3. No, the absence of impaction is worrisome, and the behavioral and social history are likely incomplete. The above pattern suggests voluntary soiling, in which a socially uncomfortable behavior is expressed to avoid an even more uncomfortable behavior, such as sexual abuse.

4. NO! The enemas may have dilated the rectum beyond the reach of the examining digit, and it is common for patients with short segment Hirschsprung's disease to pass the softer stools of breast feeding but have trouble with formula and pureed food. Expert radiographic evaluation is necessary, and the assistance of a pediatric surgeon or gastroenterologist may be helpful.

5. This is the typical appearance of the delayed view in a patient with Hirschsprung's disease. The obstruction is of high enough a grade that the portion of the colon with normal ganglion innervation has set up a "to and fro" pattern of peristalsis, evenly mixing the remaining barium with the increased fluids present in the lumen, rather than transporting the barium to the rectum where the excess fluid is removed (which is the appearance of the normal colon).

Chapter IX.9. Hirschsprung's Disease
Walton K.T. Shim, MD

An infant male presents in the second day of life with a large bilious emesis. He had been "spitty" for a day and had yielded 15 ml of greenish gastric aspirate at birth. He had not passed meconium for the first 36 hours of life. He was born at term weighing 3.5 kg.

Exam: VS T 37.2 (rectal), P 125, R 30, BP 75/55, weight 3.4 kg. He is an active hungry infant with a moderately distended abdomen. Bowel sounds are very active but not obstructive in nature. No organs or abdominal masses are appreciated and no herniae are present. His anus is patent.

An abdominal series reveals large dilated loops of bowel but no air in the rectum. A hand injected contrast enema on the third day of life shows no distinct transition zone. A 24-hour delayed film shows retained contrast and a rectal mucosal suction biopsy reveals an absence of ganglion cells and the presence of hypertrophied nerve fibers consistent with a diagnosis of Hirschsprung's disease.

Rectal irrigations are not successful in decompressing the colon leading to the establishment of a descending colonic ostomy, placed under biopsy guidance. When the infant achieves a weight of 7 kg (15 pounds) a definitive resection will be performed.

Hirschsprung's disease (also known as congenital megacolon or congenital intestinal aganglionosis) is a disease condition most commonly affecting the rectosigmoid portion of the colon. It presents with constipation in older infants and children, but mainly by distention and vomiting in newborn infants. The affected segment lacks ganglion cells which aid in normal peristalsis. Without these ganglion cells, normal peristalsis is lacking, resulting in a functional obstruction. This produces a proximal dilated colon and a distal normal appearing segment. Classically, there is an obvious transition zone where the dilated colon (with normal ganglion cells and peristalsis) meets the non-dilated colon (which is abnormal and aganglionic). The appearance is paradoxical, and in the past, has led surgeons to remove the grossly dilated (normal) portion rather than the normal appearing aganglionic segment of the colon. This of course resulted in recurrence of the obstruction and dilatation. The severity of Hirschsprung's disease varies with the length of the involved segment and may be very difficult to diagnose especially in the ultra short segment disease because of the variability of the constipation. Total aganglionosis of the colon is quite uncommon but aganglionosis involving the small bowel is rare.

The earliest description of a case of congenital megacolon was by Fredrick Ruysch in 1691, almost two centuries prior to the classic description of the Danish physician Harald Hirschsprung who reported two cases of young boys dying with a hugely dilated proximal colon and a narrowed distal colon and rectum in 1886.

Early in the history of the disease attention focused on the hugely dilated proximal colon as the abnormal portion so that resection of this area was attempted. Of course this failed soon after operation with resumption of a megacolon.

A pediatric surgeon, Orvar Swenson, was the first to devise a procedure based on observations that a colostomy established in the dilated segment functioned normally but again became obstructed when reconnected to the distal narrow portion. He concluded that functional obstruction occurred in the narrower but normally appearing distal segment. Swenson followed up these observations with pressure measurements through colostomies in patients both with and without Hirschsprung's disease and showed normal peristaltic activity in the proximal dilated colon but no peristalsis in the distal narrowed segment (1). His contribution was to resect the distally narrowed area and connect the dilated segment to two or three centimeters of distal rectum. The procedure was successful and described in 1948 (2).

This was followed a few years later by Duhamel who incorporated a portion of the anteriorly placed aganglionic rectum with a posteriorly placed, normally innervated colon to produce a new rectum composed of half aganglionic and half ganglionic musculature.

A still later modification was proposed and used by Soave who stripped the mucosa from the distal aganglionic rectum and passed the normally innervated colon through the sleeve of dysfunctional rectum (an endorectal pull-through) relying on the normal portion to propel through the abnormal cuff.

Each of these procedures has been successful in overcoming the functional obstruction in the great majority of cases, but each has its own complications.

Common to each procedure is post-operative enterocolitis characterized by abdominal distention, loose foul smelling stools, and vomiting. It occurs in a quarter to a third of cases and should be treated early and aggressively with rectal irrigations, anal dilatations and intravenous support as death may occur if it is neglected (3). Although fever and signs of infection may be present, stool cultures are often not helpful. The author routinely has parents or caregivers dilate the anus or irrigate the rectum postoperatively for several months to prevent enterocolitis. Most patients continue to improve bowel control for several years postoperatively (4).

About five percent of Swenson procedures experience anastomotic leaks. Incomplete emptying of the aganglionic portion of the pouch plagues some Duhamel patients. Patients with endorectal Soave procedures suffer from cuff abscesses and may require continued dilatations.

Recently with the introduction of minimally invasive procedures involving laparoscopic dissection and various stapling devices, techniques have changed but the basic concepts for overcoming the non-relaxing, functionally obstructive distal colon are unchanged.

The diagnosis is suggested in a term newborn who has emesis and abdominal distention early in the newborn period. Since a newborn usually passes his/her first meconium on the first day, the most suggestive symptom is the lack of meconium passage during the first day of life. Ninety-nine percent of normal newborn infants pass stool within the first 48 hours of life (5). A digital rectal examination is not helpful and may prevent an accurate contrast enema study, although a temperature probe may be gently inserted to prove anal patency.

In the face of delayed meconium passage, vomiting and abdominal distention, an abdominal series should be obtained. In congenital megacolon, intestinal dilatation is usually present with a gasless rectum. A hand injected contrast enema should be obtained to outline the rectum and sigmoid colon. Particular attention should be directed at not overfilling the intestines, thus obscuring the transition zone.

Infants with Hirschsprung's disease frequently retain contrast material longer than 24 hours and this delayed passage strongly suggests the diagnosis despite the absence of a definite transition area. Absence of ganglion cells as the cause for uncoordinated peristalsis was correctly identified as the cause for Hirschsprung's disease in infancy in1938 by Robertson and Kernahan.

Although the gold standard of diagnosis is the histological absence of ganglion cells and hypertrophied autonomic nerves, the typical radiographic transition zone between the proximal dilated and distally narrowed colon is sufficient evidence for the diagnosis in the face of supportive presence of delayed meconium passage, vomiting, and distention. Histochemical patterns with special staining techniques have also been correlated with ganglion cell absence.

Occasionally an older child presents with a history of long standing constipation requiring enemas and other attentive measures directed at producing defecation. In such cases the diagnosis is made by contrast enema as the transition zone is usually easily demonstrated. Contrast enemas in infants less than two months old may be non-diagnostic in over 20% of cases (6). In these instances when clinical and radiographic findings are unable to make a definitive diagnosis, a rectal biopsy becomes necessary. A full thickness biopsy should have an absence of ganglion cells in Auerbach's plexus located between the circular and longitudinal muscle layers. Although ganglion cells are more plentiful in this area, the full thickness biopsy complicates later surgical dissection so a rectal mucosal suction biopsy of Meissner's plexus located in the muscularis propria (i.e., performed more superficially and less invasively) is the preferred biopsy technique. Although ganglion cells are more sparse, the associated presence of hypertrophied nerve fibers is diagnostic.

Ganglion cells are absent in the most distal two centimeters of the normal rectum which is of importance when performing the biopsy and in the determination of an ultra short segment Hirschsprung's (i.e., the rectal biopsy should ideally be obtained proximal to this region).

The normal physiologic pressure in the anal canal during defecation involves a decrease in internal sphincter pressure (relaxation) with rectal distention, thus allowing passage of the fecal bolus. In a baby with Hirschsprung's disease this relaxation of the involuntary internal sphincter does not occur, thus providing another means of making the diagnosis by ano-rectal manometry.

The most frequently involved areas of aganglionosis are the rectum and sigmoid, with decreasing incidence progressing cephalad. Total aganglionosis of the colon is a rarity, and small bowel involvement is even less common.

The incidence of Hirschsprung's disease is about 1 in 5000 births with a 4:1 predominance in males. There is a familial inheritance factor greatest among siblings but less common among children of parents with the disease. It is one of the most common causes of infant intestinal obstruction and is exceeded only by intestinal atresia, malrotation and meconium ileus (in Caucasians). Hirschsprung's disease mutations have been mapped to RET protooncogenes at 10Q11.2, the recessive EDNRB gene at 13Q22, its ligand endothelin 3 (EDN3) and glial cell line-derived neurotrophic factor (GDNF) in humans. Although the majority of cases are multigenic or multifactorial, there are some conditions associated with Hirschsprung's disease such as Down's syndrome, Waardenburg syndrome, neurofibromatosis, neuroblastoma, pheochromocytoma, the MEN2B syndrome and others. The trypanosome causing Chagas' disease is responsible for an acquired form of aganglionosis which may affect not only the colon but the esophagus and heart as well.

There have been described a limited number of Hirschsprung's patients with neuronal intestinal dysplasia that may explain continued post-operative morbidity. The diagnosis of neuronal intestinal dysplasia is not easily made but is associated with abnormal neural elements and their distribution in both the submucosal (Meissner's) and intermuscular (Auerbach's) plexus. This may explain some cases of continued post-operative constipation. Since ganglion cells are of neural crest origin, other conditions affecting the physiology, distribution and migration of these cells may be related to Hirschsprung's disease (7).

Questions

1. True/False: A digital rectal examination carefully performed is most important in the diagnosis of Hirschsprung's disease in a newborn infant.
2. True/False: Post operative diarrhea from enterocolitis is a common occurrence.
3. In a newborn infant with abdominal distention and/or vomiting, what is the most significant clinical finding to raise the suspicion of Hirschsprung's disease?
4. True/False: In a child over a year of age with a radiographic transition zone, a rectal biopsy is required for a definitive diagnosis?
5. What cell line differentiates into Auerbach's and Meissner's plexus and may be responsible for other associated neurological defects?

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Answers to questions

1. false
2. true
3. No meconium for the first day of life.
4. false
5. neural crest cells

Chapter IX.10. Gastrointestinal Bleeding and Peptic Ulcer Disease
Ken Nagamori, MD

Upper GI Bleeding

Case 1: The parents of a 3 year old who you have been following since birth for biliary atresia, call to report a "nosebleed" (epistaxis) overnight. Closer questioning discloses that what they are calling a nosebleed is simply a puddle of blood found on the pillow. Having anticipated this potential complication, you ask them to meet you in the Emergency Department. There you find him to be in no distress, with no tachycardia or diaphoresis. You can find no site of bleeding in the nose or pharynx, and you also note his ascites has disappeared and his spleen seems smaller than when you saw him last week. What's going on?

Case #1 described above illustrates the one exception to the rule in large volume bleeding. In children with varices and ascites (both arising from portal hypertension) the acute volume loss from the bleeding can be repleted by 'auto-infusion' of the ascites. Portal hypertension triggers ascites at relatively low pressures (10-12 mm Hg), and the volume depletion from bleeding results in enough reduction in the portal pressure to coax the fluid back into the circulation. The hypovolemic state accounts for the loss of the previously existing splenomegaly. These patients also illustrate that all blood loss is whole blood and that the hemoglobin and hematocrit will not fall until they are volume repleted with crystalloid or plasma. Cirrhotic patients with ascites are the only ones where the acute CBC may be a better indicator of the volume lost than vital signs at presentation.

His hemoglobin is 7 (hct 21). His INR is 1.2. He continues to be in no acute distress and he is able to go directly to endoscopy, having requested 2 units of packed RBCs to be available in the OR for emergency transfusion if needed, with more packed RBC and fresh frozen plasma standing by. A small ulcer is found in the distal esophagus, with an associated gastric varix. There are two other fully distended esophageal varices which are band ligated, and while sclerotherapy is considered for the gastric varix (the banding is impossible to accurately apply in this location) you elect to watch as it appears to be thrombosed and plans are made to return for a repeat endoscopic inspection and treatment as needed in a week or two. He tolerates the procedure well with no complications, and after talking with his parents, you call his transplant specialists to update them on his situation.

Gastrointestinal bleeding covers a wide topic, and is best managed by subdividing it into smaller and smaller entities. But even before making the first obvious decision as to whether it's "upper" or "lower" GI bleeding, the first step is to make a rough assessment as to how MUCH bleeding is going on. In pediatrics, the best single vital sign for assessing acute volume depletion is the heart rate rather than the blood pressure, since infants, children and adolescents have a huge reserve capacity for increasing cardiac output by increasing the heart rate. Thus, the blood pressure begins to fall only in late shock. Orthostatic change in the heart rate is a useful sign (only occasionally unreliable), since a difference of 10% or more may indicate substantial acute volume depletion. Another sign to look for are cool extremities, often with a relatively sharp demarcation between cool and normal skin temperature, as an indication of peripheral vasoconstriction. These signs are applicable to acute volume depletion from any cause (such as vomiting and diarrhea) and not just to acute bleeding. As with any pediatric life support issue, the first steps in assessment and management are to verify airway, breathing, and circulation (ABC). Acute volume depletion requires rapid volume replacement and determination of the source of loss.

When there is a significant difference between the degree of volume loss from either end and the apparent normal state of the intravascular volume, the next step is to verify the material as blood and that it is indeed coming from the patient. Here are some anecdotal examples: 1) A child whose bright red diarrheal stools are closer in color to the red-orange of the food dye of the fruit punch that he has been guzzling during his acute gastroenteritis than to any blood color you've ever seen (i.e., the "bloody" diarrhea is really fruit punch). 2) The robust, demanding, overfed infant whose mother has mastitis and whose hematemesis is actually coming from his mother's blood loss (i.e., swallowing mother's blood from a bleeding nipple) rather than his own. 3) The newborn whose mother had placenta previa and a particularly bloody delivery whose hematemesis again is ingested maternal blood and not his own. The first example often is resolvable during the initial phone conversation. The third can be identified reliably by performance of an Apt test for fetal vs adult hemoglobin, but the second often requires careful history taking and examination to exclude intrinsic GI bleeding.

Converse consideration must also be given to those who present with signs of acute intravascular volume depletion (especially impending shock) and NO signs of bleeding discernible externally. The GI tract can easily hide a loss of blood amounting to a substantial portion of the total intravascular volume. Processes with high rates of bleeding, particularly if beyond the stomach (making them less prone to hematemesis) must be considered. Such lesions include (but are not limited to) duodenal ulceration with arterial bleeding, duodenal varices or varices at small bowel anastomotic sites (in the case of children with surgical hepatoportoenterostomies), small bowel vasculitides, hemobilia (bleeding in the biliary tract), and enteric duplications (including Meckel's diverticula) with secretory mucosa and secretory products that lead to ulceration.

The next step is to verify that the bleeding is indeed coming from the GI tract, in part to determine whether the following algorithms will be applied, but also as reassurance that the volume of any recurrent bleeding is not likely to be high or is likely to be easily managed. Epistaxis is a common cause for moderate volume bleeding (some epistaxis blood is swallowed and then vomited as hematemesis) and is more common than peptic ulceration as a cause of hematemesis and melena. Always check the anterior portion of the nasal septum for evidence of blood and ulceration indicative of bleeding. Application of direct pressure for 5 minutes (by the clock) to allow for good clot adherence and retraction (no peeking or the clot will lift off and the bleeding will resume) during any recurrent bleeding episode, is usually all that is necessary. Cautery typically causes more problems than it solves. Topical antibiotics can be used to treat nasal impetigo if that is the cause of the epistaxis. Dental and oral bleeding typically is smaller in volume and is usually identifiable on close inspection. Anal fissuring is technically a "GI" lesion, but the risk of rebleeding is low and its generally benign nature differentiates it from the lesions below. Here, the bleeding is typically bright red, and can be painless (though more often associated with pruritus at the anus or cramping prior to the passage of a larger caliber formed stool). Passage of clots is possible if the fissure extends internal to the internal anal sphincter. But the differentiating hallmark is any continued dripping of blood into the toilet after the formed stool has passed (and the internal anal sphincter has closed) or the persistence of bright red blood on the toilet paper for more than 2-3 wipes. Either of these indicates the presence of the lesion outside the internal (but potentially proximal to the external) anal sphincter. Good inspection requires gentle separation of the buttocks, best attained in the decubitus position with the knees up against the chest. The goal is to open the external anal sphincter, often attainable by having the patient take a slow deep inhalation. The fissure is identifiable as the red or white-based linear ulcer, usually anteriorly or posteriorly positioned. Specific attention should be paid to whether the margins appear undermined (traumatic fissures have simple vertical margins, while the anal lesions of Crohn's disease and the vasculitides are caused by the undermining of the subcutaneous supportive structures).

Once it is verified the patient is indeed losing blood from their GI tract, but is stable, attention turns to specific diagnosis. Here again subdividing the possibilities is helpful, with the next step being the semi-artificial conceptual one of "upper" vs "lower" tract bleeding. With the provisos of the preceding paragraphs accounted for, hematemesis is a reasonable indicator of an UGI source. Conversion to "coffee grounds" is not necessarily indicative of a gastric source since any blood placed in acid for even a few seconds converts to acid hematin (brown color), and conversely if the acid is neutralized or is otherwise not present for any reason, the blood will not convert (and will be red). On the other hand, melena is only an indicator of bleeding in an area bathed in acid, and while this usually indicates the upper GI tract, other sites of acid production such as a Meckel's diverticulum (with acid secreting ectopic gastric mucosa) or occasionally acid fermentation in the right colon can trigger the same chemical conversion. And conversely, the absence of melena in the bleeding does not preclude an UGI site, since brisk bleeding from an arterial source in the duodenum, plus the rapid transit times of infants and younger children, and their lower acid secretion rates can result in passage of blood per anus that is still nearly bright red.

Quantification of the bleeding seen is of some help diagnostically, as is the presence or absence of associated symptoms and signs. Further stratification by age helps establish probabilities:

Newborns are not old enough (not enough time) to develop full peptic ulceration. Coagulopathy due to liver cirrhosis is possible, but rare. Neonates under the intense physiologic stresses that would place them in an NICU setting typically develop gastric erosions rather than deeper gastric ulceration or they can hemorrhage from DIC. Even vitamin K deficiency of infancy takes time to develop.

Infants have had time to develop some, but not all of the ills that befall older children. Again mechanical trauma to (or other lesions of) oral structures will result in small to medium amounts of hematemesis and are far more common than the erosions of severe reflux esophagitis or frank ulceration of the stomach or duodenum. The latter lesions are usually suspected by signs of dyspepsia, including (but not limited to) crying, irritability centering around feedings, colic, drooling, eructation (belching), and vomiting. The preverbal infant and young child often will not be able to adequately indicate the associated pain, and peptic disease is therefore more often not identified until there is significant vomiting or even frank hematemesis. Allergic gastroenteritis more commonly first appears in the first few months of infancy though eosinophilic gastritis can be identified at any age. Though more commonly presenting as failure to thrive, allergic gastroenteritis can occasionally present with hematemesis or other evidence of upper (and lower) GI tract bleeding.

In toddlers most of the above processes continue, but their added mobility increases the possibilities for mechanical issues, including ingested caustic agents (lye, tile cleaner, electric dishwasher detergent) or acids, and foreign bodies. A toddler presenting with signs of partial esophageal obstruction (inability or unwillingness to swallow solids) and intermittent hematemesis warrants a radiographic evaluation to establish the absence of a lodged foreign body and if no clear history is obtainable regarding of the duration of the lodgment, caution is to be exercised in its removal, since penetration of or even embedding in the wall of the esophagus or adjacent structures (e.g., vena cava or aorta) is not uncommon. Ingestion of button batteries is another special consideration in the case of foreign bodies since the lithium ones can retain sufficient charge as to cause significant mucosal burn even when they appear to be dead, while the mercury, silver, and alkaline button batteries usually do not.

In older children, a Mallory-Weiss tear (esophageal tear) or an erosion caused by prolapse of a portion of the gastric cardia (typically along the lesser curvature) is far more common than nonspecific gastritis, erosion (esophageal or gastric), or frank ulceration as a cause of UGI bleeding. Such bleeding usually follows a period of protracted and usually forceful vomiting, and is usually relatively limited in volume (a few teaspoons), but it can be profuse. A rectal examination with stool which is negative for occult blood helps verify the observed short duration of the process. Esophageal erosion typically is preceded by complaints identifiable as peptic in origin in pediatrics and is rarely present in a pain free setting, which requires an extensive burn. In the case of the older child or adolescent with this presentation, consideration needs to be given to NSAID-induced gastropathy arising from self-medication. The lesions are typically erosions arising from the disruption of mucosal cytoprotection due to the broader inhibition of prostaglandin synthetase. The incidence is low compared to the widespread use of these medications and the increase in the absolute rate of this complication reflects the increasing use of these medications in the over-the-counter setting.

Upper GI bleeding etiologies by age:

Age	Small volume	Medium volume	Large volume
Newborn		Gastric erosion (in NICU setting)	Ingested maternal blood, vitamin K deficiency, DIC.
Infant	Mechanical trauma, allergic or other gastritis, reflux esophagitis, ulcer.	Same as infant, plus oral lesions and ulcerations (rare).	
Child	Dental/oral source, hemoptysis, gastritis (non-allergic), reflux/chemical esophagitis, (beware of foreign body).	Same as infant, plus epistaxis, Mallory-Weiss tear/erosion, peptic ulcer.	Varices, arterial bleeding from ulcer, DIC.

Frank peptic ulceration remains uncommon as a source of bleeding during most of childhood and adolescence. Helicobacter pylori can play a role, and by itself, can cause bleeding from gastritis, though far more commonly it presents as a non-bleeding distinctive nodular gastropathy with preference for the antrum. While breath testing using labeled urea is identified as showing promise in establishing the diagnosis, the North American Society of Pediatric Gastroenterology and Nutrition's position is that endoscopy remains the only reliable means of establishing and refuting its presence, and that blood testing, due to poor specificity, is of little utility (1). In that regard, the low probability of Helicobacter gastritis in this age group even in the face of proven duodenal ulceration means that for each child appropriately identified by serologic testing, there will be several falsely labeled, and extension of this testing into evaluation of those who simply present with hematemesis or even just pain raises the likelihood of identifying false positives.

However, in true hemorrhage from the upper GI tract (defined as bleeding sufficient to require volume repletion with blood), peptic ulceration, variceal bleeding, and DIC are the most common causes. Of these, variceal bleeding is the most frightening, since blood loss rates can approach total blood volume within an hour or less. Varices arise from portal hypertension, which in turn arises most commonly

from cirrhosis (e.g., biliary atresia as in case #1), but can also arise from extrahepatic obstruction of the portal vein. They most commonly present in the distal esophagus but may also be found in the gastric cardia or in the duodenum, where they can be far more difficult to treat. They represent an enlargement of the submucosal venules as a means of rerouting the blood flow from the portal to systemic venous circulation (a porto-systemic shunt) and the degree of portal hypertension required to establish the shunt is only minimally higher than that which would produce splenomegaly or ascites, making these physical findings important in the evaluation of the hemorrhaging patient. Identifying patients at risk for this prior to hemorrhage is far preferable, and a routine search for these findings should be undertaken at every office visit of any patient being followed for a process that can lead to cirrhosis (such as biliary atresia in the case presented). The bleeding is typically painless, as the vessels are superficial to the muscular layers and the erosion that starts the bleeding is therefore particularly shallow. The initial (or "herald") bleed may be surprisingly small as the vein rapidly collapses and clots, but the dislodgement of that clot can be followed by particularly voluminous bleeding. Endoscopic examination for diagnosis and treatment either by banding or injection of sclerosing agents is the preferred acute management once volume repletion has made sedation or anesthesia possible, and while a trans-jugular intrahepatic portovenous shunt placement (TIPS procedure) may be palliative, the only "cure" is resolution of the underlying cirrhosis (by transplantation) for those with intrahepatic disease conditions. Those with cavernous transformation of the portal vein typically will create other intraabdominal shunts in locations which do not bleed so profusely if they can be carried into the second half of the first decade.

The myriad causes of upper GI bleeding prompt usage of a layered strategy to the diagnostic process. With the above history parameters and physical findings indicating that: 1) the patient is (at least temporarily) hemodynamically stable, 2) no clear site of bleeding external to the GI tract as an alternate source to explain the bleeding, 3) no known lodged esophageal foreign body, 4) medium to moderate bleeding in whom the presumed risk of later hemorrhage is worth giving serious consideration; the next step is placement of a naso-gastric catheter to assess the volume of blood that has not been regurgitated, and more importantly, to identify (or refute) any ongoing bleeding. A large-bore tube is recommended, as clots may need to be removed, and the orogastric (rather than nasogastric) route may facilitate evacuation. Gastric lavage with normal saline at body or room temperature is more comfortable. Icing of the saline is not required and in smaller patients, may produce significant hypothermia. Gastric sampling and lavage may be omitted if variceal bleeding is suspected and endoscopy is already planned, but the hemorrhaging patient typically otherwise deserves both procedures. The gastric sampling and lavage serves to identify the patient who has indeed bled briskly from the upper GI tract or who may still be bleeding, and who will need to go on to immediate endoscopic examination. In contrast, the patient whose bleeding is suspected as coming from a non-intrinsic or otherwise low-risk source does not require immediate endoscopy. A negative gastric aspirate in a patient who is otherwise only suspected of an upper GI bleeding site because of passage of melena and who has no hematemesis would prompt a search for alternate sites of acid-associated bleeding such as a Meckel's diverticulum.

Gastric aspiration will only rarely be falsely negative. This would typically occur in patients who are bleeding from a deep ulcer in the duodenal bulb with sufficient pylorospasm to prevent any regurgitation of blood into the stomach. These patients can easily be mistaken to have a Meckel's diverticulum with acid-secreting ectopic gastric mucosa and secondary ulceration as they too may present with volume depletion and melena but no hematemesis, and if suspicion is otherwise high (primarily due to tenderness to epigastric palpation) and/or larger volumes of bleeding, endoscopy is warranted anyway.

Endoscopy offers both diagnostic and therapeutic advantages, and typically is much more sensitive than radiographic evaluation of the upper GI tract as most hemorrhaging lesions are still superficial. Radiographic contrast studies are dependent on identification of a moderate-sized ulcer crater, and lack sensitivity in identifying risks for rebleeding such as a visible vessel or adherent clot. Even varices are difficult to identify radiographically, and endoscopy offers the ability to intervene to reduce the risk of rebleeding via variceal band ligation or intravascular injection of a sclerosing agent. Likewise, ulcers and other lesions at significant risk for resumption of hemorrhage may be addressed thermally or chemically through the endoscope.

Peptic ulcer disease is most accurately diagnosed by endoscopy. Referral to an endoscopist (usually a gastroenterologist) facilitates diagnosis and treatment since treatment regimens which consist of a□
cimetidine, ranitidine, etc.), proton pump inhibitors (e.g., omeprazole) and antibiotics for H. pylori create numerous therapeutic option combinations. Optimal therapeutic decision making for pediatric patients with peptic ulcer disease is best left to gastroenterologists who are most familiar with the most recent studies and recommendations.

If endoscopy fails to identify the bleeding lesion, further investigation of the hemorrhaging patient includes radionuclide scanning and angiography. Radiographic intervention can include selective intraarterial embolization as well as the TIPS (trans-jugular intrahepatic portovenous shunt) procedure, but a full discussion of this is beyond the scope of this chapter in basic diagnosis, as the choices are typically guided by the pediatric gastroenterologist involved in the endoscopic procedure above (2,3,4,5).

Lower GI bleeding

Case 2: The parents of an otherwise robust 3 year old boy call with a frantic report of bright red bleeding per anus. Pain is denied, as are fever, malaise, or rash. The toilet bowl seems filled with blood and clots, but the anus wipes clean with one swipe and no further blood is seen. You are able to convince them to come to the office instead of heading for the ER. In the office, the child is in no distress and wonders what all the fuss is about. His vital signs are normal for age, and physical examination shows no abnormalities, including external inspection of the anus with the child in the knee-chest position on his left side to enable full exposure of the anus down to the internal anal sphincter. What do you do next?

The patient who presents with bleeding only from the anus produces a separate (but overlapping) diagnostic tree. The presence of melena hints at an upper GI tract origin, but is simply indicative of passage of the blood through acid, which can arise in the presence of acid secreting ectopic gastric mucosa in any enteric duplication, of which the most common is a Meckel's diverticulum, or occasionally if the cecum is particularly acidic due to fermentation. Conversely the absence of melena does not exclude an upper GI tract origin if the transit time is sufficiently short or the acid is otherwise neutralized or not present and the bleeding is brisk enough.

As discussed in the patient who presents with hematemesis, the initial evaluation centers around rapid estimation of the volume of blood lost and the risk of ongoing or recurrent bleeding. Again the problem is best stratified into ages and rates of loss.

As with upper GI bleeding, the neonate has fewer diagnostic possibilities since most problems take a while to develop fully. While any infection (bacterial or viral) can lead to sufficient mucosal inflammation ranging from punctate bleeding to gross hemorrhage and DIC, necrotizing enterocolitis is almost unique to the neonatal period. In other respects, resembling ischemic injury in the older child or adult, the process in the neonate does more commonly include submucosal pneumatosis, implying compromise of the mucosal barrier. It usually presents with other signs of intestinal obstruction, partial or complete, and bleeding is typically one of the lesser findings, and is most

commonly occult. It presents more commonly in the severely premature, but can afflict term infants who have a preceding clinical problem that predisposes them to bowel ischemia (such as polycythemia or birth asphyxia). Refer to the chapter on necrotizing enterocolitis.

Allergic enteropathy is more typically a problem of the young infant, as the inflammatory process is acquired and requires time to set up. It typically presents before 2 months of age with either occult or gross bleeding, and typically is accompanied by failure to thrive and/or a moderate degree of mucus in the stool to suggest widespread mucosal irritation. Involvement of the proximal GI tract (the stomach and small bowel) more commonly results in slow weight gain, signs of poor enteric motility (vomiting) and other signs of gastric stasis and protein losing enteropathy. Involvement of the colon is associated with mucusy stools laced with blood. In the latter, a Wright stain may be helpful only if it shows sheets of eosinophils, but a firm diagnosis rests on mucosal biopsy showing widespread nests of eosinophils in the submucosa rather than the scattered eosinophilia seen in more nonspecific inflammation. A clinical diagnosis may be made by rapid and complete resolution of the symptoms by elimination of the offending protein either by a return to exclusive breast feeding or substitution of a properly hydrolyzed formula (e.g., Nutramigen, Pregestimil, Alimentum). A switch to an alternate allergenic protein source (soy, goat's milk, etc.) during a period of sensitization may result in further reactivity and only true hypoallergenic feedings are to be allowed. Widespread reports, laboratory research, and personal experience indicate that while generally hypoallergenic, maternal breast milk may contain identifiable fragments of cow's milk protein from the maternal diet in quantities sufficient to trigger a reaction. Personal experience suggests the quantity needed in the maternal diet is substantial, and typically lies outside routine dietary parameters, however maternal exclusion of dairy products may be undertaken in the case of stubbornly persistent (and typically low-grade) inflammation. If allergic enteropathy (gastroenteropathy or colitis) is encountered, firm exclusion of the offending protein is to be undertaken for the entire first year of life in hopes of eliminating the clone of sensitized lymphocytes. This involves reading the ingredient panel of every item the child will eat, looking for "non-fat dairy solids" or "non-dairy" creamers (which contain powdered milk protein). If a soy allergy is present, the prohibition shifts to soy, including soy sauce and tofu. Typically the exclusion is not complete, and if (repeated) inadvertent exposure shows no sign of reaction, the restrictions can be lifted. But recurrent reactions can be severe if of the acute hypersensitivity (type I) variety. This can result in sufficient vomiting and diarrhea to cause significant volume depletion, and if uncertain as to the residual reactivity, a formal staged dietary challenge with nursing support (i.e., this may need to be done as an inpatient or in an observation unit) may be needed at one year of age before the offending food may be safely reintroduced in quantity.

Another cause for minor bleeding per anus that is unique to infancy is nodular lymphoid hyperplasia. It typically presents with punctate bleeding best characterized as streaks of blood with small streaks of mucus in otherwise normal stool in an otherwise thriving infant. The number of streaks and the amount of blood do not vary with fecal texture. This compares to infection, allergy or other more generalized inflammatory processes of the distal bowel where loose stool indicates inflammation, and therefore goes hand in hand with more mucus and blood. The only time the bleeding disappears in nodular lymphoid hyperplasia is in the face of liquid stools, in which case the streaks of mucus and blood are dissolved in the diarrhea but can be found by occult blood testing. Nodular lymphoid hyperplasia can readily be identified by proctoscopic examination which typically demonstrates a rectum that is studded with submucosal nodes measuring 2 mm across with central ulceration. The bleeding comes from the ulceration and the intervening mucosa is completely normal in appearance, explaining the disparity between the texture of the stool, the amount of bleeding and the normal growth of most of these infants. This permits exclusion of allergy and infection as possible causes since these typically cause more widespread inflammation, visible in the rectum of infants presenting with visible blood and mucus in the stool. Nodular lymphoid hyperplasia is a benign, self-limited process associated with the age-appropriate hypertrophy of the lymphatic tissue of the enteric submucosa. In some infants, the central portion of the overlying mucosa undergoes punctate ulceration. The cause of the process remains unknown. What is known is that the process normally becomes dormant during the latter half of the first year as the nodes regress in size (and activity), and though there may be occult blood found in the stool for the remainder of the first year, there is little likelihood of anemia and no association of any later enteric disease process. As such, my usual recommendation is to continue with routine feedings, introducing solid foods at the usual times as the process is not allergic in origin. The hemoglobin may be checked slightly more frequently than your usual schedule for age, and iron supplementation should be started only if it drops significantly. Inability to keep up with iron loss is atypical enough to warrant reassessment of the original diagnosis.

Toddlers in turn have a cause for chronic occult bleeding and often times severe anemia which is unique to their age range in overconsumption of milk. The lactoferrin of cow's milk has an extremely high affinity for iron, higher than anything in the human iron transport system, and it typically is not saturated in milk as routinely sold (but it is saturated in infant formula). Lack of an alternate iron source and excessive intake of milk can result in severe iron depletion, and as iron is also required for maintenance of gut mucosal integrity, the process accelerates as the iron stores fall. Hemoglobins of 4.0 gm/dl are not uncommon in this setting, and if tested, the stools may be positive for occult blood. The diagnosis is made by a detailed diet history, and verification of the extremely low iron stores. The cure is effected by a return to a truly regular diet for age with reasonable milk intake and a sufficient source of iron, though an occasional patient will require transfusion.

Processes that can cause small but visible quantities of bleeding at any age are dominated by infection, though anal fissures are even more common, as described previously. The most common worrisome organisms include Campylobacter, Salmonella, Shigella, and enterotoxigenic E coli, but other routine pathogenic bacteria and protozoans can be acquired from contaminated food and standing water sources. The first 4 are routinely included in culture screens for enteric pathogens (the rest are not). Campylobacter can cause a severe colitis which is identified more often now that CT scanning is the preferred method for identification of appendicitis in the patient presenting with crampy abdominal pain. The degree of thickening of the submucosa and muscular layers can be mistaken for transmural thickening indicative of Crohn's disease, with the pain and bloody diarrhea adding to this diagnostic possibility. But a normal ESR in the proper clinical picture suggests a pause in the rush to colonoscopy and therapy until the culture results are available, since the process clears rapidly with erythromycin treatment. Shigella also warrants antibiotic therapy if found, and while treatment of Salmonella may raise the risk of producing a chronic carrier state, since most carriers arise from colonization of the gallbladder, cautious treatment with an agent concentrated in bile (such as trimethoprim/sulfamethoxazole) if the organism is sensitive may be warranted in the patient with ongoing or severe symptoms. The one organism whose treatment with antibiotics or antispasmodics is to be avoided is enterotoxigenic E. coli (such as E. coli O157). Use of these agents can produce enough enterotoxin release as to trigger Hemolytic Uremic Syndrome. Antibiotics should be held until the offending bacteria is positively identified, and even over the counter antispasmodic agents are to be avoided.

The immune suppressed patient presents a particular challenge, for in addition to the above agents one needs to consider atypical organisms such as cytomegalovirus and Mycobacterium avium intracellulare (MAI), which can produce severe bleeding with transmural lesions scattered throughout the bowel and colon. Epstein-Barr virus can cause lymphoproliferative disease with chronic low-grade blood

loss and more of a protein losing enteropathy picture. Typhlitis also occurs in the patient recovering from neutropenia as the new granulocytes are preferentially directed toward the inflamed cecum. These processes are rare in the immune competent patient.

Enterocolitis due to Hirschsprung's disease can occur both prior to and after surgical repair. The latter instance is indicative of stricture at the anastomotic site and recurrence of functional obstruction. As a stasis phenomenon it can also be seen in those with ileorectal pouches and other anastomosis, and while it can cause bleeding, it usually presents with explosive, foul diarrhea. For evaluation of the infant presenting with enterocolitis as the first manifestation of Hirschsprung's disease, see the chapter on constipation. Hirschsprung's disease itself is covered in a separate chapter.

Other processes that can cause moderate bleeding volumes, usually as part of a broader clinical picture include general obstructive processes such as intussusception, volvulus, and other mechanical issues that can cause focal bowel ischemia. They usually present with other signs of obstruction, typically with an acute onset of crampy abdominal pain that cycles every 10 to 60 minutes as the major migrating motor complex passes through the obstructed segment. Waiting for the passage of currant jelly stool (bloody stool) before considering intussusception in the differential diagnosis is to be discouraged since this is a late finding. Early radiographic evaluation with plain films is to be encouraged. In fact, the possibility of intussusception should be considered when any type of blood in the stool is encountered.

In patients presenting similar to the above, but with lesser signs of obstruction, consideration should be given to vasculitis, far more commonly due to anaphylactoid (or Henoch-Schonlein) purpura than to Systemic Lupus Erythematosus. The typical presentation is dominated by crampy pain with a usually minor bleeding component. In the case of anaphylactoid purpura, the platelet count may be high, but the ESR is typically in the normal range, in contrast to the elevation seen in SLE or to EBV-induced lymphoproliferative disease, both of which can mimic the radiologic picture of HSP. Treatment with corticosteroids is discouraged until these entities and lymphoma or leukemia are more definitively ruled out.

Inflammatory bowel disease (IBD) typically presents with a history of chronic but nonspecific signs. Poor weight gain and especially linear growth can be noted as much as 6 months before onset of cramping and bleeding, though there are hyper-acute variants of ulcerative colitis. These entities are covered in detail in a separate IBD chapter but for the purposes of this discussion, IBD can produce anything from occult bleeding to florid bloody diarrhea. In ulcerative colitis, the blood and stool texture are inversely related, with both mucusy diarrhea and bleeding being indicators of inflammation. Crohn's disease, more commonly affecting portions of the GI tract other than the rectum, can present with unremarkable stools, but will also produce mucusy diarrhea if the distal colon is involved. A quick check of the oral mucosa and anus for the undermined vasculitic lesions seen in either site can be diagnostic of Crohn's disease. A detailed family history searching for other versions of autoimmune disease can be supportive diagnostically, for while it is rare to have another with IBD in the family, there is often a strong family history of other autoimmune manifestations.

And finally, among the (relatively) common causes of colonic bleeding, polyps are to be considered whenever there is a report of painless bleeding of apparently moderate volume. Solitary juvenile polyps are the most common, and typically do not become large enough to cause bleeding before the end of the second year. As hamartomas, they are extremely vascular but have no sensory tissue and bear essentially no neoplastic risk as long as they are indeed solitary. The familial polyposis syndromes produce diffuse adenomatous polyposis, resulting in studding of the mucosa with often nearly confluent polyps, all of roughly the same size. These carry a significant neoplastic risk, and were until recently, an indication for early colonic resection, but experience with NSAIDs (particularly sulindac) in adults has been extended to children in causing regression of the visible lesions. It remains to be seen if this significantly reduces the long-term neoplastic risk, but it seems to permit a reduction from the every-other-year colonoscopy surveillance often undertaken in the second decade. The diagnosis of polyps (single or multiple) starts with the history of painless bright red bleeding, generally without anemia despite a protracted history, and no anal fissure on inspection. Digital rectal examination is usually diagnostic as most solitary polyps arise within the last 2 inches of the rectum, and the familial adenomatous polyposis syndromes result in many small polyps within reach. Gardner's syndrome is associated with unusual retinal pigmentation in affected individuals and may also present with osteomas, though these usually are more prominent in the second decade while the small but visible bleeding usually appears by the middle of the first decade. Peutz-Jeghers syndrome is associated with pigmentation in unusual sites (buccal mucosa, the webbing between fingers and toes) but like the other multiple hamartomatous polyp syndromes, PJ typically does not present with bleeding. Therapy for isolated polyps is endoscopic removal and for multiple polyps is endoscopic sampling to establish a diagnosis. Waiting for a polyp to autoinfarct will not permit specific identification as to type, and the presence of more than 3 polyps, even with a "juvenile" type histology, is still associated with a higher risk of eventual colon cancer. Recent advances in genetic screening in the diagnosis and management planning of the familial adenomatous polyposis syndromes in pediatrics was recently discussed in detail in reference #6.

Lower GI bleeding etiologies by age

Age	Small volume	Medium volume	Large volume
Newborn	Infection, necrotizing enterocolitis		Ingested maternal blood, sepsis, DIC
Infant	Fissure, allergy, infection, nodular lymphoid hyperplasia	Same as infant plus volvulus intussusception, other bowel obstruction and/or ischemia	DIC, peptic or other ulceration, Meckel's diverticulum, CMV, MAI (esp. with HIV)
Child	As above plus IBD (Crohn's disease), cow's milk protein sensitivity (with severe iron deficiency), EBV (esp. immunosuppressed)	As above plus HSP and other vasculitides, typhlitis (immunosuppressed)	All of above plus polyp(s), IBD (ulcerative colitis)

In summary, identification of "lower" GI bleeding is even more dependent on the history and characterization of the bleeding than that from the upper GI tract, and can be confounded by "upper" GI sources. Even with hemorrhage, patients rarely become significantly

volume depleted on an acute basis and in most instances there is enough time to perform appropriate testing, including culture, in a sequential manner. Many times, the workup of the crampy patient with modest bleeding in loose mucusy stools involves a quick survey of inflammatory markers and a 2 to 3 day wait for the culture results from the rectal swab. A rectal swab has a superior yield over culture of stool material because the center of the lumen (i.e., stool material) typically contains dead or less viable organisms, while the viable enteric pathogens are closer to the mucosa and are more readily sampled by brushing the rectal wall. If the ESR is low in the face of thrombocytosis and a history of crampy pain, particularly in a patient with any dermal lesions, a small bowel series may demonstrate the characteristic "thumb-printing" of localized mucosal edema typical of HSP and enable early administration of corticosteroids. Otherwise, if the ESR is high and the growth parameters are low, once the culture results are found to be negative, the next step is colonoscopy to look for lesions indicative of IBD. On the other hand, finding a solitary polyp on initial examination permits a relaxed scheduling on a more elective basis both for the physician and the family.

For case #2, our patient's presentation with painless bleeding of apparent moderate volume yet without signs of significant volume depletion is indicative of a polyp. Rectal examination finds a single 1 cm pedunculated polyp 2 cm from the anal verge. Colonoscopy is scheduled, as the prep for even proctoscopy for polypectomy requires stringent removal of all stool to prevent a short-circuit current and an unintended burn, and a search is to be made for further polyps. The gastroenterologist reports no others are seen and the polyp in question has been easily removed by an electrocautery snare. Histologic analysis verifies a juvenile polyp, and no followup is planned.

Questions

1. You are called to the nursery where you are shown a burp cloth with loose clots of regurgitated blood. The newborn in question is sleeping quietly, with completely normal vital signs and no sign of tenderness or other bleeding when examined. You recall his mother presented with placenta previa. What do you do next?
2. At a two month well baby visit, his parents bring in a diaper double-bagged because of the foul odor. The stool is tarry and tests positive for occult blood, but the child appears particularly robust, having gone from a birth weight of 7 pounds 1 ounce to his current weight of 12 pounds 10 ounces. He is somewhat fussy and demanding of feedings, and his mother complains of getting no rest as she has to feed him hourly. Recently, her left breast has become quite sore and there is intense pain when he nipples. On examination, the infant is colicky, but there is no abdominal tenderness and his vital signs are also within normal limits with no adjunct signs of intravascular volume depletion. What is going on?
3. 3 year old presents with melena but no hematemesis, and no abdominal pain. How do you evaluate him?
4. Melena is usually indicative of upper GI bleeding. Indicate how this can sometimes be due to lower GI bleeding.
5. Red blood per rectum is usually indicative of lower GI bleeding. Indicate how this can sometimes be due to upper GI bleeding.
6. A 14 year old female has yet to show secondary sexual development which you have always attributed to excessive involvement with the school track team. However in the last 6 months her finishing times on the mile (her favorite event) have steadily lengthened from second best in the state to this week's race where she could not finish. She presents today complaining of loose stools, streaked with blood. How do you work up her illness?
7. A 3 year old boy presents to the emergency department passing bright red blood per anus. He is diaphoretic and tachycardic (120 supine, 140 upright) and complains of generalized abdominal pain. You are unable to localize tenderness but are comfortable that there is no rebound tenderness and he is not at risk of perforation. Placement of an NG tube to lavage his stomach is negative. By the time you have given enough crystalloid to replete his blood volume, his hemoglobin has dropped to 7 grams. Since his summer physical 2 months ago had included a hemoglobin of 12, you realize he has indeed lost a substantial portion of his blood volume over a short period of time. He is admitted to the hospital, where over the next two days as you wait for the stool culture results. He requires 250 cc transfusions daily to maintain his hemoglobin and you realize that the brisk bleeding continues. The stools remain bright red. What do you do next?

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Answers to questions

1. A modified Apt test can be done. Take the loose clots and suspend them in a minimal amount of tap water (you need a visibly pink supernatant composed of free hemoglobin, hence the tap water to lyse the cells). Centrifuge the cells and to 5 cc of pink supernatant add 1 cc of 1% sodium hydroxide. Read in two minutes: adult hemoglobin turns yellow or brown, fetal hemoglobin remains pink. If the supernatant turns yellow, the blood is mother's, and every one can relax.
2. This infant has no sign that the bleeding originates with him, as bleeding sufficient to produce melena should leave him quite shocky. The history gives every sign that he has induced a mastitis (and nipple bleeding) in his mother, and she is able to compensate for the several ounces of blood loss that produced the melanotic stool. You counsel her on proper feeding and handling techniques to keep the infant satisfied without having to overfeed, and have his mother avoid feeding on the affected side until the inflammation subsides. At followup in a week, all are smiling.
3. ABC's first. He shows no sign of acute intravascular volume depletion, but looks a little pale and turns out to be mildly anemic, indicating a longer standing problem. Next, place an NG tube to look for upper GI bleeding but you find no evidence of this. Now what? There is evidence of bleeding in an area bathed in acid, but it is not the stomach (or the duodenum). If he is hemodynamically stable, you have time to pretreat with a histamine-2 receptor blocker to improve the yield of a Meckel's scan looking for ectopic gastric mucosa. This finds a hot spot in the lower mid-abdomen which the technician assures you is not tracer in the bladder. You contact your pediatric surgeon for minimally invasive removal of a presumptive Meckel's diverticulum with acid-secreting ectopic gastric mucosa.

4. The black color is due to blood exposure to acid. Acid fermentation can take place in the cecum. If this occurs and the transit time is relatively slow, bleeding in this area can present as melena. Bleeding from a Meckel's can also result in acid exposure in the lower GI tract.

5. The acid level in the stomach is low (possibly due to antacids and H2 blockers) and/or the bowel transit time is very rapid. Also, the bleeding may originate from the duodenum which does not expose the blood to acid if the pylorus is tight or the level of stomach acid is low.

6. The history has all the hallmarks of inflammatory bowel disease, but still the common things are more common. The physical examination shows no weight loss (but little net gain over the year), and she has a mild temperature elevation (100.5 degrees) and tachycardia (105) but no specific findings in the abdomen other than a mild increase in the amount of fluid and gas palpable in the small bowel and colon. Along with the CBC and ESR, you obtain a rectal swab for stool culture. There is no anemia, but the WBC count is slightly elevated and the ESR is 6. You are puzzled until the stool culture results return 2 days later, positive for Campylobacter. You call to discuss the results and find her new puppy had been ill the week before (dogs can both harbor and become ill from this organism), and the poor race performance actually arose because she was getting fed up with her coach (her father) and had been wanting to quit. Since she is still out of school with the cramping and diarrhea, you start her on erythromycin, offer to act as a go-between on the issue of changing sports, and annotate her chart to remind yourself to monitor for other signs of depression in the future.

7. As the negative gastric aspirates over the last 2 days indicate no UGI source, you prep him for colonoscopy to look for a lower GI bleeding site. GoLYTELY is used in hopes of diluting the bleeding as blood rapidly absorbs all light even in a thin film, and you anticipate much suctioning and lavage which will markedly extend the time for the procedure. As he will be under anesthesia anyway, you also obtain consent for EGD for completeness' sake. At endoscopy, the EGD study finds the pylorus is tightly shut as there is a large duodenal ulcer (not a simple erosion) with a visible vessel (an indicator of high risk of recurrent bleeding). With this you joyfully cancel the colonoscopy as being unnecessary, and chalk up the experience as a reminder that rapid transit times and the low acid production of early childhood can sometimes prevent the blood from encountering enough acid to turn to acid hematin or melena. Indeed, the higher the volume lost, the more acid is needed and the less likely the reaction. Unfortunately, as the finding was a therapeutic surprise, you are unprepared to address the ulcer in any invasive manner (sclerotherapy, heater probe, etc.) and have to return the patient to intensive care on an IV histamine receptor blocker and carafate and sufficient antacid to keep the pH of the gastric contents, measured every hour, above 6.5 (and well above the 4.5 activation level of pepsin). Preparations are made to return with the proper equipment the next day if he continues bleeding, only to find the bleeding stops with the procedure (and the drop in splanchnic pressures encountered under anesthesia), the current measures are more than sufficient, and no further transfusions are required. The patient makes a rapid and full recovery, with no recurrence in over 5 years (based on actual personal experience).

Chapter IX.11. Inflammatory Bowel Disease
Alan K. Ikeda, MD

This is a 16 year old female who presents with fever and diarrhea. Further questioning finds that she has had similar episodes in the past few years, but none as severe as the current episode. She does not weigh herself regularly so weight loss could not be confirmed. However, she does admit that her clothes feel somewhat looser than last year. Her menstrual periods are regular. Her last menstrual period began two weeks ago.

Exam: VS T 37.0, P 85, RR 18, BP 100/65, oxygen saturation 100% in room air. Height is at the 50th percentile. Weight is at the 5th percentile. She is a thin appearing female in no acute distress. HEENT exam is significant for slightly tacky oral mucous membranes. Her eyes are not sunken. Neck is supple without lymphadenopathy. Her heart has a regular rhythm, but slight tachycardia with no murmurs. Her lungs are clear with good aeration. Her abdomen appears scaphoid. There are mildly hyperactive bowel sounds with diffuse vague abdominal pain without any point tenderness. No masses or organomegaly are noted. Her extremities are cool to at the distal limbs, but warm and dry otherwise. Her pulses are good with brisk capillary refill. No rashes are noted. Her breasts and genitalia are Tanner stage 3-4. Rectal exam demonstrates non-specific discomfort without masses or severe tenderness. Her anus is normal externally. Her stool is guaiac positive.

A CBC shows mild microcytic, hypochromic anemia and thrombocytopenia. Wright's stain of the stool for fecal leukocytes is positive for WBCs, but no eosinophils. Stool, blood and urine cultures are obtained.

Inflammatory bowel disease (IBD) is a term that is used to describe chronic inflammatory diseases of the gut. It usually refers to Crohn's disease and ulcerative colitis.

Crohn's disease (CD) is also known as regional enteritis. The disease is described as discontinuous (regional) areas of transmural inflammation that affect any part of the GI tract (mouth to anus). Ulcerative colitis (UC) is described as a process that results in diffuse superficial colonic ulceration.

Although there are some discrepancies over previous misdiagnoses of IBD as infectious gastroenteritis, most experts agree that the incidence of UC has increased over the first half of the 1900s. Since then, the prevalence of UC has plateaued, while Crohn's disease has increased during the 1950s-1980s. The incidence of UC, as compared to CD is similar worldwide. Both have an increased prevalence in the Northern regions of the world. The two diseases are prevalent in North America, northwestern Europe, and in the United Kingdom. This is in comparison to the decreased rates in Southern Europe, South Africa, and Australia. IBD is rare in Asia, Africa, and South America.

UC and CD are both diseases of late adolescence and early adulthood. However, there have been documented cases of IBD diagnosed in infancy and childhood. The incidence of UC is equal in the male and female gender. Crohn's disease is more common in females than males by 20-30%, but in the younger pediatric age groups, males have a greater incidence. Caucasians, especially Ashkenazi Jewish, have a greater risk than other ethnicities.

Although the precise mechanism of IBD is still unknown, there is a general consensus that it is multifactorial. There is currently no known infectious agent that has been identified/isolated, which reproducibly causes IBD. Still, infection may be a "triggering event" for an acute episode of IBD. Viruses and Mycobacterium paratuberculosis are some of the organisms that have been studied.

Genetics is a likely contributor in the pathogenesis of IBD. In CD, monozygotic twins have a concordance rate of 44%, while just 4% in dizygotic twins. UC has less of a genetic preponderance as monozygotic twins have a concordance rate of 6% to 25%. There are multiple studies attempting to isolate the gene(s) involved in this disease that are beyond the scope of this chapter.

Dietary components have also been studied. No toxin or antigen has been isolated. In a retrospective study, CD has been associated with "westernization" of the diet or an increased of intake of animal proteins, total fat and animal fat.

Some interesting modulating factors are the protective effects of breastfeeding against CD and appendectomy against UC. Cigarette smoking increases the risk for CD while it decreases the risk for UC.

The big picture is that multiple events have an additive effect that results in an abnormal mucosal immune response, which leads to intestinal inflammation. If this inflammatory response is not well regulated, then chronic IBD develops.

Common Comparative Aspects of CD and UC:

Description	Crohn's Disease	Ulcerative Colitis
Location	Mouth to anus 60% ileocolic 30% small intestine 10% colonic	Colon only
Abdominal mass	common	rare
Perianal disease	common	rare
Strictures	common	unusual
Fistula	common	unusual
Risk of cancer	increased slightly	increased greatly
Histology	Transmural inflammation Skip areas Aphthoid lesions Fissuring ulceration Granuloma Fibrosis	Mucosal inflammation Diffuse involvement Crypt abscesses Crypt distortion
Microscopic	Edema, increase in mononuclear cells in the lamina propria. Again, the hallmark is transmural extension into the bowel wall and adventitia.	Active UC: Neutrophils in the mucosa, goblet cell mucus depletion, and clumps of neutrophils in crypt lumens.
Clinical Presentation	Abdominal pain Anemia Weight loss Falling off growth curve Delayed puberty Perianal lesions Finger clubbing	Bloody, mucusy diarrhea Lower abdominal cramps (less common) Abdominal tenderness Vomiting Fever Weight loss

Crohn's Disease commonly presents with crampy abdominal pain, recurrent fever, weight loss, and diarrhea. Abdominal pain is diffuse and more severe than in UC and often worse in the lower right quadrant. Rectal bleeding is seen in about a third of the cases. Weight loss, poor weight gain, anorexia, and delayed growth occur in 40% of cases. This growth abnormality may present as short stature and/or delay in sexual maturation. Perianal disease may be the presenting complaint. Further examination may show a fistula, skin tags, or recurrent abscesses.

Ulcerative colitis presents with bloody stools, abdominal pain, and tenesmus. 100% of cases present with bloody mucinous stool. Mild disease is defined as less than 6 stools per day, no fever, no anemia, and no hypoalbuminemia. Moderate disease is described as more than 6 stools per day, fever, anemia, and hypoalbuminemia. 90% of cases present with mild to moderate disease. Severe disease exhibits high fever, abdominal tenderness, distention, tachycardia, leukocytosis, hemorrhage, severe anemia, and more than eight stools per day. Rare complications that may arise include toxic megacolon and intestinal perforation.

Extraintestinal complications of IBD may involve the joints (arthralgias are more common than arthritis), integument (erythema nodosum and pyoderma gangrenosum), eyes (episcleritis, uveitis, and rarely, orbital myositis), hepatobiliary system (sclerosing cholangitis, chronic active hepatitis), pancreas (pancreatitis), renal system (nephrolithiasis, hydronephrosis), coagulation system (hypercoagulability), and bone (decreased bone density).

The diagnosis is based on clinical presentation, radiologic findings, endoscopy with mucosal biopsy, and exclusion of other causes. Since corticosteroids will likely be used for treatment, stool cultures are done to rule out infectious causes. The stool may need to be evaluated for tuberculosis and schistosomiasis. Double-contrast barium enema may show diminished colonic haustrations in UC. In CD, it may identify nodularity, skip areas, a string sign, and fistula formation. Colonoscopy is superior to evaluate the large bowel because of its increased sensitivity and biopsy capability for histologic assessment.

Hematologic findings may exhibit anemia and thrombocytopenia. Further studies may show specific nutritional deficiencies including iron deficiency, hypoalbuminemia, and elevated transaminases. There have been recent advances in serologic testing, which in addition to screening for IBD, can differentiate between CD and UC. Anti-neutrophil cytoplasmic antibodies (ANCA) and anti-Saccharomyces cerevisiae antibody (ASCA) are laboratory tests that are used to serve this purpose. ANCAs are immunoglobulin IgG antibodies that are directed against neutrophil cytoplasmic components. Initially ANCAs had been studied in Wegener's granulomatosis

and necrotizing vasculitis. By utilizing immunofluorescence studies, UC can be identified as it demonstrates perinuclear staining (pANCA). The test is specific in separating IBD from infectious colitis and other GI disorders. Unfortunately, the sensitivity is only 50-65%. ASCAs are IgG and IgA antibodies that bind to mannose sequences in the cell wall of S. cerevisiae strain Sul. The specificity and sensitivity of this test is also suboptimal. It is positive in 55-60% of people with CD and 5-10% of those with other GI disorders. Its low sensitivity and specificity have kept these studies from replacing definitive radiologic and endoscopic studies. The tests are also limited in the cases where they are most needed. In CD limited to the colon, the pANCA may also be positive. ASCA is also less likely to be positive in CD limited to the colon. Thus, the dilemma remains in which the clinician attempts to distinguish UC from CD involving the colon only.

Sulfasalazine is the usual treatment for mild to moderate UC and Crohn's disease of the colon. Sulfasalazine is not effective in small bowel CD. In moderate to severe UC and Crohn's disease of the small bowel, corticosteroids are used. Care must be taken to rule out bacterial causes of diarrhea prior to starting systemic corticosteroid therapy. Severe UC is treated with hyperalimentation, high dose corticosteroids, sulfasalazine, and cyclosporine. Corticosteroids may result in growth retardation. Metronidazole is used to treat perirectal fistulae in patients with CD. Metronidazole is used for both active disease, as well as prevention of recurrence. Azathioprine and 6-mercaptopurine are immunomodulating drugs which are used to reduce inflammation of the intestines, so that the corticosteroid doses can be reduced. Cyclosporine and tacrolimus inhibit cell-mediated immunity. Anti-TNF-alpha is a newer intervention that may be beneficial.

Surgical resection is indicated when there are intractable symptoms despite medical therapy, intestinal complications, intra-abdominal abscesses, bowel-bladder fistula, perforation, and/or hemorrhage. Surgical resection does not necessarily result in a cure. In some patients, elective colectomy is performed to reduce or eliminate the risk of colon cancer.

Crohn's disease may be subdivided into 3 categories: 1) The fistulizing type may form fistulas that are entero-enteric (between bowel segments), bowel-bladder, enterocutaneous (bowel to skin), perianal fistulas, and/or intra-abdominal abscess. 2) Patients with fibrostenosing disease have persistent abdominal pain and radiologic findings consistent with stenoses of the small or large intestine. 3) The inflammatory category includes patients who do not fit either of the two diseases or had been in one category and now fit in another. As listed above, growth impairment may occur either secondary to the illness or to therapy.

Death in CD is rare in children. Adults with Crohn's colitis may have the same risk for cancer as do patients with UC. The overall risk for colorectal cancer is 8% after twenty years of disease. This risk is increased in those affected by perianal disease. Most patients undergo resection of the affected segment within 20 years, which decreases the overall incidence of carcinoma.

Ulcerative colitis is also divided into 3 categories, which include mild, moderate and severe disease. One large study noted 70% of children entering remission by three months despite their initial severity level. The greater the severity of the disease, the greater was the likelihood of undergoing a colectomy. Nine percent and 25% those with moderate to severe disease underwent colectomy by 1 and 5 years, respectively.

After 10 years of disease, the risk for colorectal cancer increases. About 12% of those with disease for 10 to 25 years will have colorectal cancer. Since there is such a high risk, regular colonoscopic surveillance is recommended, which identifies colorectal cancer at a potentially curable stage 65% of the time. However, these biannual examinations that start at 7-10 years of disease were not found to be cost effective. A more sensitive, specific and reliable screening test is currently being sought.

Questions

1. What portion(s) of the GI tract are affected by CD versus UC?
2. Which IBD has a greater association with cancer?
3. What are the common histologic findings in CD and UC?
4. Name three extraintestinal findings in IBD?
5. Describe the three types of CD and UC.

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Answers to questions

1. CD affects the gut anywhere between the mouth to the anus, while UC affects the colon.
2. UC has a greater risk for cancer. CD only slightly increases the risk for cancer.
3. CD: Transmural inflammation, skip areas, aphthoid lesions, fissuring ulceration, granuloma, fibrosis. UC: Mucosal inflammation, diffuse involvement, crypt abscesses, crypt distortion.
4. Joints: arthralgias are more common than arthritis. Integument: erythema nodosum and pyoderma gangrenosum. Eyes: episcleritis, uveitis, and rarely, orbital myositis. Hepatobiliary system: sclerosing cholangitis, chronic active hepatitis. Pancreas: pancreatitis. Renal system: nephrolithiasis, hydronephrosis. Coagulation system: hypercoagulability. Bone: decreased bone density.
5. Crohn's disease may be subdivided into 3 categories: 1) The fistulizing type, 2) Patients with fibrostenosing disease, and 3) The inflammatory category. Ulcerative colitis is divided into three categories: mild, moderate, severe.

Chapter IX.12. Malabsorption Conditions
Max C. Miranda

A 15 year old girl presents to the physician's office with a three year history of intermittent diarrhea. Further history reveals a past history of anemia, anorexia, and minor abdominal pain. Her weight has been the same for 3 years now. Her mother has attributed this to her having a "rough time in school". Her mother also questions whether the symptoms could be related to a recent move from their home state of Minnesota. She has not yet reached menarche. A diet history suggests a normal diet with adequate iron intake. Her family history is negative for malabsorption and inflammatory bowel disease.

Exam: VS T 37.5, P98, R 18, BP 110/70. Ht 145 cm (57 inches), wt 35 kg (78 pounds), both less than the 5% percentile. She is alert, active and cooperative. She is thin and small for age but not cachectic. HEENT: Her conjunctivae are pale. Her teeth are pitted and discolored. Her neck is supple without adenopathy. Her heart and lungs are normal. Her abdomen is slightly protuberant and hyperresonant. Bowel sounds are slightly hyperactive. Tanner stage 4 for both breasts and pubic hair. Examination of both hands reveal mild pallor and flat fingernails. She is able to ambulate and no neurologic deficits are noted.

Because of her small size and amenorrhea, a bone age reveals a 3 year delay and suggests osteopenia. A stool examination is negative for blood and reducing sugars. The 72-hour fecal fat study shows a moderate increase in fat content. A CBC shows a mild anemia. Her reticulocyte count is low and her iron studies indicate the presence of iron deficiency. An ESR is normal, making the possibility of inflammatory bowel disease less likely. Her small size, the steatorrhea and the iron deficiency all suggest the possibility of some type of GI malabsorption condition. An upper GI study with small bowel follow-through is normal. A chloride sweat test for cystic fibrosis is normal. A lactose breath hydrogen test showed an elevation in hydrogen of 40 ppm, suggesting carbohydrate malabsorption. An upper GI endoscopy shows no visible abnormalities; specifically, no ulcers or hemorrhage. Biopsies from the duodenal and proximal jejunal area reveal severe villus atrophy consisting of a flat mucosa with deep crypts and no evidence of Giardia lamblia. A serologic human anti-tissue transglutaminase ELISA test came back positive for autoantibodies suggesting the diagnosis of celiac disease.

She is started on a strict gluten-free diet. She responds dramatically and upon follow-up is now reporting an increased appetite and improved mood. She has remained symptom free for about a year now. She has also noticed a resurgence in her growth and has reported menarche that started about a month ago.

Gluten-sensitive enteropathy, also known as sprue, celiac sprue and celiac disease, is one of the many causes of malabsorption. Malabsorption is a clinical term for the entire spectrum of conditions occurring during digestion and absorption of ingested nutrients by the gastrointestinal tract. Perturbations in the digestion and absorption of food nutrients can occur either in the luminal phase, the mucosal phase, or the transport phase of the ingested food. Classifying the many entities of malabsorption in this manner makes it easier to understand their exact mechanisms. Causes of malabsorption can be explained by the way the disease process interferes with the normal digestive and absorptive mechanisms.

Malabsorption encompasses conditions that go from a single nutrient malabsorption (e.g., lactose intolerance) to pan malabsorption (e.g., cystic fibrosis and celiac sprue). Celiac sprue is a disease that predominantly affects people of European descent (rare in people of African and Asian ethnicity), and currently has a frequency of 1 in 5000 in the US (although this frequency is debated and some feel that this frequency may be much higher). Celiac disease is manifested variably by malabsorption to different types of nutrients. While presenting symptoms such as diarrhea and weight loss are common, the specific cause of malabsorption should be established using physiological evaluations. In celiac sprue, suggestive screening investigations include steatorrhea that denotes fat malabsorption, decreased d-xylose absorption found in carbohydrate malabsorption, and serological markers such as antigliadin antibodies or the new ELISA test for anti-tissue transglutaminase. The treatment of the underlying disease is often dependent on the establishment of definitive cause for the malabsorption. In the case described, gluten-sensitivity is the underlying cause. Were it not for the logical steps followed by the clinician, the quite dramatic resolution of symptoms brought about by denying the patient food devoid of gluten would not have happened if the exact etiology was missed.

As emphasized before, the causes of malabsorption can be best appreciated if they are classified into the specific phase of digestion and absorption that is disturbed.

1. The luminal phase is where dietary fats, proteins, and carbohydrates are hydrolyzed and stabilized by digestive enzymes and bile. Diseases often associated with this phase include:

- Enterokinase and trypsinogen deficiencies that can lead to protein malabsorption.
- Impaired micelle formation that can cause problems in fat stabilization and the resulting fat malabsorption due to deconjugation of bile salts in bacterial overgrowth.
- Stasis of intestinal content due to a variety of factors (motor and anatomic abnormalities, small bowel contamination from enterocolonic fistulas) can cause bacterial overgrowth.
- Bacterial overgrowth can also cause decreased luminal availability of substrates (carbohydrates, protein, vitamins).

2. The mucosal phase relies on the integrity of the brush border membrane of intestinal epithelial cells to transport digested products from the lumen into the cells.

- Impaired brush border enzyme activity may lead to lactose intolerance and sucrase-isomaltase deficiency.
- Impaired nutrient absorption can be inherited or acquired deficits. Inherited defects include glucose-galactose malabsorption, a-betalipoproteinemia, and Hartnup disease.
- Acquired defects which are more common may be caused by decreased absorptive surface area (intestinal resection), damaged mucosa (celiac sprue, tropical sprue, giardiasis, Crohn's), or an infiltrating disease of the intestinal wall (lymphoma, amyloidosis).
- Tropical sprue and Giardiasis are two mucosal phase abnormalities due to damaged intestinal mucosa. Tropical sprue, a syndrome characterized by diarrhea, weight loss, and malabsorption, occurs in residents or visitors to the tropics and the subtropics, usually in connection with certain geographical areas such as Southeast Asia and the Caribbean. The pathophysiology is poorly understood but is theorized to be caused by an acute intestinal infection that leads to jejunal mucosal injury. The disease is primarily a disease of adults but it is also described in children.
- Giardiasis like celiac sprue has symptoms characteristic of panmalabsorption. The organism, Giardia lamblia is a protozoan that appears to alter intestinal epithelial structure and function leading to malabsorption. Giardiasis usually begins with ingestion of the cyst

that eventually leads to trophozoites in the stomach and duodenum. High-risk groups include travelers, homosexual men, individuals with immunoglobulin deficiency states, and children, especially those who attend day care centers.

3. Transport (removal) phase malabsorption abnormalities may be caused by lymphatic obstruction or vascular insufficiency.

The signs and symptoms of malabsorption depend on the specific cause or etiology, and the specific nutrient deficiency that ensues. Age also plays a big factor. Malabsorption causes a far more acute and wide-ranging symptomatology in younger children than in the older child. Diarrhea is the most common symptomatic complaint which might lead to dehydration, especially in younger patients. In older children, weight loss and fatigue might be more pronounced. Some patients may try to compensate by increasing caloric consumption, making the diagnosis more difficult. Children in the pubertal ages may display disturbance in anthropometric growth (weight, height, weight by height) and pubertal development. Other symptomatology that follows from specific components of disturbed digestion and absorption include:

Steatorrhea: Most often due to fat malabsorption.
Flatulence and abdominal distention: Release of gas by bacterial fermentation of undigested or unabsorbed food particles.
Edema: Commonly from chronic protein malabsorption or loss of protein into the lumen.
Anemia: Depending on the cause, can be micro or macrocystic, such as Fe deficiency anemia secondary to celiac disease.
Bleeding disorders and ecchymosis: Usually a result of vitamin K malabsorption.
Bone defects: Can be due to vitamin D deficiency or calcium malabsorption.
Neurological manifestations: Electrolyte disturbance or specific vitamin malabsorption such as B12 neuropathy.

A malabsorption condition usually contains a specific physical manifestation (e.g., growth, weight, and pubertal disturbance). Growth and developmental charts are extremely helpful in diagnosis. A physical examination should look into the possibility of finding specific signs of individual nutrient malabsorption to aid in the organization of symptoms.

General: Orthostatic hypotension, weight loss, muscle wasting, loss of subcutaneous fat, pallor, ecchymosis.
HEENT: Alopecia or thinning hair, pale conjunctiva, aphthous ulcers, cheilosis, glossitis, dental hypoplasia, abdominal distention, tympanic abdomen, hyperactive bowel sounds, ascites.
Hands: Koilonychias (flattened or spoon shaped nails), pale skin.
Neurologic: Motor weakness, peripheral neuropathy, ataxia, Chvostek or Trousseau's sign due to hypocalcemia or hypomagnesemia, numbness, paresthesias.
Musculoskeletal: Mono or polyarthropathy, back pain, muscle weakness.

After the initial examination, a physician may have a reasonable idea of a diagnosis. Often, laboratory investigations are needed to confirm the cause.

Stool analysis: Quantitative stool fat analysis for 72 hours, consistency, pH (due to acidic stools in the presence of fermented sugars and reducing sugars in carbohydrate malabsorption), stool bile acids (increased in bacterial overgrowth syndromes), presence of large serum proteins (such as alpha-1-antitrypsin, may indicate a protein-losing enteropathy, ova and parasites (for Giardia), testing for chronic intestinal infections (such as C. difficile or Cryptosporidium), consistency, fecal leukocytes (such as in inflammatory bowel disease), and occult blood.

Screening Lab Tests: CBC (for anemia), blood smear (for abnormal blood morphologies that may indicate vitamin B-12 deficiency, amyloid, or a-betalipoproteinemia), urinalysis (urine may reveal unusually high concentration of malabsorbed substance since, in many cases, the kidney and the gut use the same transporter such as in glucose transporter deficiencies where urinary glucose will be elevated while the serum level is normal), total protein (decreased in protein malabsorption), albumin (decrease may indicate severe malnutrition or pancreatic insufficiency), liver function tests (in liver and biliary diseases), calcium and phosphorus levels (to determine vitamin D deficiency which might be present in gross steatorrhea), serum immunoglobulins (for autoimmune enteropathies), sweat test (for cystic fibrosis), and radiographic bone age (especially in pediatric patients).

Other lab studies to be considered include: Schilling test (for B12 deficiency), urinary 4-hydroxy phenylacetic acid (shown to be elevated in the urine of children with bacterial overgrowth syndrome; enteric bacteria that posses L-amino acid decarboxylase produce 4-hydroxyphenylacetic acid from dietary tyrosine), fat-soluble vitamin assays for fat malabsorption, LDL cholesterol (may be lower than normal with bile and malabsorption), ESR and C-reactive protein (may be elevated in inflammatory bowel disease), serum bile acids (congenital deficiency in the sodium-bile cotransporter results in primary bile acid malabsorption, which may appear as diminished reabsorption of bile acids in the kidney), GI motility studies (can be as simple as an upper GI contrast study or as complex as the performance of antroduodenal motility studies, depending on the need, which can recognize damage or abnormalities present in the gut due to inflammatory and infective processes), breath hydrogen analysis and, d-xylose absorption study (to specify carbohydrate malabsorptions), carbohydrate oral tolerance test (for specific carbohydrate digestion and absorption dysfunctions). IgG and IgA antigliadin and IgA antiendomysial antibodies are present in gluten-sensitive enteropathy. The presence human antitissue transglutaminase ELISA has a reported sensitivity of 96-100% and specificity of 99-100% and now appears to be the new criterion standard for screening of sprue.

Barium radiographic studies (upper GI series) can be useful in assessing anatomy and function. Endoscopy performed by a gastroenterologist permits direct visualization of the mucosal surface. During the endoscopy procedure, mucosal biopsies can provide histological information, identification of infective organisms and functional assays of the biopsied tissue for specific enzymes.

Medical management of underlines two basic principles: 1) Treatment of the etiology of malabsorption. 2) Correction of nutritional deficiencies.

Treatment of malabsorption is as varied as the etiologies that cause them. The intestine appear to repair itself slowly, thus treatment may require a longer course. Since many of the conditions that are caused by malabsorption, respond well to specific remedies, the need to make an accurate diagnosis becomes even more important. Most treatments highlight the dramatic effect of correcting the underlying defects of digestion and absorption. An example would be the gluten-free diet instituted in patients with gluten sensitivity. The effects of strict adherence to this diet include the full reversal of the disease process. Treatment of diarrhea with oral gentamicin or an appropriate broad-spectrum antibiotics that includes anaerobic coverage (e.g., metronidazole) reverses bacterial overgrowth and chronic infections, resulting in a rapid improvement in the patient's function. Specific malabsorption syndromes that include enzyme deficiency or imbalance

can be successfully managed with oral supplements. The use of lactase supplements or non-lactose containing milk substitutes is beneficial in lactose intolerance. Pancreatic lipase can be replaced with oral supplements to improve fat digestion.

Efficient absorption of essential nutrients will not occur if the diarrhea is still present. Usually, the complete withdrawal of the offending substance can correct diarrhea. Care should be taken to avoid the iatrogenic elimination of necessary nutrients. For example, in celiac disease, gluten withdrawal is often enough to correct the symptoms. Carbohydrates and other foodstuff not continuing gluten can continue to be consumed.

Correction of nutritional deficiencies is the other important treatment goal. Dietary modifications and supplementation are especially useful if one considers the slow self-repair process of the severely damaged intestines. Dietary changes should be individually tailored to the individual and the underlying cause of malabsorption, but in general, a high protein, low fat diet is recommended. Decreased fat intake also reduces steatorrhea. The dietary modifications closely parallel the essence of withdrawing certain offending food products in the diet and promoting adequate calorie intake. Vitamin, mineral, and trace element deficiencies should be sought and corrected. Supplementation of nutrients whose absorption and digestion mechanisms were disturbed is essential. Anemia should be treated with appropriate supplements and specific deficiencies corrected by oral (or parenteral) supplementation. Fat-soluble vitamins may be required for a patient with severe steatorrhea.

Questions

1. What are the three phases of digestion and absorption discussed in this chapter?
2. Dietary fats, proteins, and carbohydrates are hydrolyzed and stabilized by digestive enzymes and bile in which phase?
3. Identify the phase in which digested food is moved from the lumen into the cells.
4. True/False: The symptoms of malabsorption are worse in older children compared to younger children.
5. True/False: Diarrhea is the most common presenting symptom of malabsorption in younger children.
6. True/False: Withdrawal of gluten-containing food from a patient with celiac disease is often enough to reverse the symptoms of malabsorption.

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Answers to questions

1. Luminal phase, mucosal phase, and transport (removal) phase.
2. Luminal phase.
3. Mucosal phase.
4. False. Younger patients often display a more acute and wider-ranging symptomatology than older children.
5. True.
6. True.

Chapter IX.13. Meckel's Diverticulum
Gareth K. Nakasone

An 18 month old male is brought to the ED by his parents with a chief complaint of passing large amounts of dark red blood from his rectum, and black jelly-like stools of two days duration. The child does not appear to be in acute distress at rest, although his parents say that he seems to sleep more and looks paler than normal over the past 24 hours. Two days ago they were alarmed by maroon-colored blood on the child's bedding and oozing out the side of his diaper. He has not cried, complained, or shown any signs of focal pain or discomfort thus far. He has not vomited and continues to feed regularly. Prior to the onset of symptoms, he is reported as having a good appetite and is a generally "healthy and active baby" with no significant PMH.

Exam: VS T 37.4 (rectal), P150, RR 40, BP 90/50, oxygen saturation 100% in room air. His weight, height and head circumference are at the 50th percentile. He is pale and quiet, lying supine on the exam table. HEENT exam is significant for pale conjunctiva and lips. His neck is supple, non-tender, no bruits, no lymphadenopathy. His heart is slightly tachycardic, regular rhythm, no murmurs, no rubs, no gallops. His lungs are clear to auscultation. His abdomen is mildly distended with possible generalized tenderness upon palpation. No inguinal hernias are noted. Testes and penis are normal. A small amount of dark red blood is present in the diaper which is guaiac positive.

Labs: WBC 7,000, hemoglobin 9.6 g/dl, hematocrit 31%, MCV 67. Bleeding from a Meckel's diverticulum is suspected. A Tc-99m pertechnetate scintigraphy scan (a "Meckel's scan") is ordered, which demonstrates an area of focal uptake in the right lower quadrant of the abdomen. This focus appears at the same time as gastric activity, and its intensity increases in parallel with gastric activity. These findings are consistent with ectopic gastric tissue in a Meckel's diverticulum.

He is given an IV normal saline infusion. A transfusion is contemplated, but held off for the time being. A surgeon is consulted, and an emergent laparotomy is performed in which a portion of the patient's ileum is resected containing a 6 cm x 1.5 cm ulcerated appendage (a Meckel's diverticulum). He recovers well postoperatively.

Meckel's diverticulum is the most common congenital anomaly of the gastrointestinal tract, affecting about 2% of the population. Meckel's diverticulum affects the distal ileum and represents the remnants of the proximal end of the embryologic yolk stalk (i.e., the omphalomesenteric or vitelline duct) which normally obliterates completely by the 8th week of gestation. While most cases of Meckel's diverticulum are asymptomatic, complications such as perforation, hemorrhage from peptic ulceration, intussusception, volvulus or intestinal obstruction are associated life-threatening disease states.

During early embryonic development, the omphalomesenteric duct connects the midgut to the yolk sac, allowing free communication between the compartments. Starting from the 7th gestational week, this duct undergoes progressive narrowing, becomes occluded, and ultimately disappears completely by the 8th week (1). For reasons not well understood, the normal obliteration of the duct fails to occur in 1-3% of the population. When this happens, possible outcomes include (2):

1. Persistence and patency of the entire tract leading to a congenital umbilico-ileal fistula (presenting as a draining fistula at the umbilicus).
2. An outpouching diverticulum secondary to persistence of the proximal part of the vitelline duct (Meckel's diverticulum) with or without a fibrous band connecting the ileum to the inner surface of the umbilicus.
3. Persistence of the duct deep to the umbilicus, forming an umbilical sinus.
4. Fluid-filled cysts (enterocystomas) either intra-abdominal or just below the umbilical skin because of persistence of the middle portion of the duct.
5. Obliteration of the lumen of the duct but persistence of the duct tissue, forming a fibrous omphalomesenteric ligament.

Meckel's diverticulum is the most common omphalomesenteric duct anomaly, accounting for 97% of reported cases (2). The prevalence of Meckel's diverticulum based on autopsy records is estimated to be 2-4% of the general population. The male:female ratio of patients with asymptomatic Meckel's diverticula is 1:1, however, males with the anomaly are 3 times more likely to develop complications at some point during their lives. Four to six percent of all Meckel's diverticula cases result in complications and classically present in infants 2 years old or younger (3).

There are a few studies suggesting familial inheritance of Meckel's diverticula, however no other evidence currently exists to support a genetic predisposition as a risk factor (4). Other congenital anomalies, such as cleft palate, bicornate uterus, and annular pancreas, have been noted in association with Meckel's diverticulum, and Meckel's diverticulum may be found more frequently in patients with Crohn's disease compared to the general population (5).

A Meckel's diverticulum is a finger-like projection located in the distal ileum, usually within 100 cm of the ileocecal valve, about 1-10 cm long, and 2 cm wide. In contrast to intestinal duplications and mesenteric cysts, a Meckel's diverticulum arises from the antimesenteric border of the bowel, has its own mesentery, and derives its blood supply from a terminal branch of the superior mesenteric artery (the embryonic right vitelline artery). It is also considered a true diverticulum as it contains all layers of the intestinal wall (2).

The mucosa of the Meckel's diverticulum is heterotopic in over 50% of all cases, with 80% gastric in origin. Although pancreatic acinar tissue, duodenal Brunner's glands, colonic mucosa, hepatobiliary, jejunal, rectal, and endometrial tissues, or a combination of these tissues is noted on occasion, heterotopic gastric mucosa is by far the most common tissue seen (6). Consequently, the ectopic gastric mucosa found in the diverticulum may form a chronic ulcer and may damage the adjacent ileal mucosa via increased acid secretion. Such peptic ulceration can lead to pain, bleeding, and/or perforation.

Meckel's is the most common cause of gastrointestinal bleeding in children. Painless melena or bright red blood per rectum is a classic presentation, but there are other presentations as well.

A few cases of large diverticula measuring up to 3.5 cm in diameter and 9 cm in length have been reported in newborns presenting with a palpable mass and intestinal obstruction (2).

The Meckel's rule of 2's (8):

1. Occurs in 2% of the population.
2. Only 2% of those with a Meckel's diverticulum will manifest clinical problems.
3. Usually located 2 feet proximal to the ileocecal valve and the diverticulum is approximately 2 inches long.
4. Symptoms commonly manifest at age 2 years.

Most Meckel's diverticula are asymptomatic and are found either during autopsy or incidentally on laparotomy, laparoscopy, or barium study for other abdominal conditions. It is controversial whether to attempt surgical correction of an asymptomatic Meckel's diverticulum found incidentally as the risk of developing postoperative complications may be as high as 8% in such cases (3).

When patients with a Meckel's diverticulum develop symptoms, a complication is almost always present. The principal complications of Meckel's diverticulum include ulceration, hemorrhage, small bowel obstruction, diverticulitis, and perforation (9).

Ulceration with subsequent hemorrhage (often hemodynamically significant, but usually not life threatening) is the most common complication, with an incidence of about 20-30% of all complications. It is more common in children younger than 2 years and in males. The most common presentation is painless hematochezia due to ulceration within the diverticulum or adjacent intestinal mucosa as a consequence of acid secretion from ectopic gastric mucosa contained in the diverticulum (6). This represents the most common cause of painless hematochezia in patients less than 2 years old. Consequently, severe anemia or hemodynamic shock affects many of these children. Gastric mucosa with peptic ulceration is found in the vast majority of these cases (10).

Intestinal obstruction is another frequent complication and is observed in 20-25% of all symptomatic Meckel's diverticula and is attributable to intussusception, volvulus (often twisting around a persisting umbilical remnant), herniation, or entrapment of a loop of bowel through a defect in the diverticular mesentery (11). Patients with intestinal obstruction due to Meckel's diverticulum are usually older and present with abdominal pain, and vomiting. In cases of intussusception, patients may also present with a palpable mass in the lower abdomen and bloody (currant jelly) stools. Radiography of the abdomen may indicate an ileus or frank stepladder air fluid levels as observed in a bowel obstruction (8).

Diverticulitis occurs in approximately 10-20% of patients with symptomatic Meckel's diverticulum and occurs more often in the elderly population. Patients may present with symptoms of intermittent, crampy abdominal pain and tenderness in the periumbilical area, indistinguishable from appendicitis. Perforation of the inflamed diverticulum leads to peritonitis while stasis in the diverticulum causes inflammation and secondary infection leading to diverticulitis. Diverticular inflammation can lead to adhesions, which can cause intestinal obstruction (2).

Umbilical anomalies occur in up to 10% of patients with a symptomatic Meckel's diverticulum. The anomalies consist of fistulas, sinuses, cysts, and fibrous bands between the diverticulum and umbilicus. A patient may present with a chronic discharging umbilical sinus, superimposed by infection or excoriation of periumbilical skin. There may be a history of recurrent infection, sinus healing, or abdominal wall abscess formation. When a fistula is present, intestinal mucosa may be identified on the skin. A discharging sinus should be approached surgically with a view toward correction. Exploratory laparotomy may be required. When found at laparotomy, a fibrous band, should be excised because of the risk of internal herniation and volvulus (12).

Neoplasm is the least commonly associated pathology and is reported in approximately 4-5% of complicated Meckel's diverticulum. Of the various types of tumors reported, leiomyoma is the most frequent tumor, followed by leiomyosarcoma, carcinoid, fibroma, sarcomas, benign mesenchymal tumors, and adenocarcinomas (2).

Plain film radiographs are rarely useful in detecting a Meckel's diverticulum, although these may be useful at identifying an intussusception or bowel obstruction. An upper GI series and barium enema are also unreliable detection modalities. In addition, barium absorbs pertechnetate and its use should never precede a 99mTc scan since this may give rise to false negative results (7).

Preoperative diagnosis of a bleeding Meckel's diverticulum is best established by a technetium-99m pertechnetate scintiscan (Meckel's scan). The isotope, administered intravenously, identifies ectopic gastric mucosa as it is readily taken up by parietal cells (13). In a positive scan, the patient develops immediate tracer localization in the stomach and in the right lower quadrant. This test has a sensitivity of about 75%, with 15% false-positive and 25% false-negative rates. Reportedly, a size of 1.8 square cm of ectopic gastric mucosa in a Meckel's diverticulum is required for a positive result. The accuracy of the Meckel's scan may be improved with the use of pentagastrin or cimetidine, which increase the uptake of pertechnetate by parietal cells (7).

False negative scans are seen in Meckel's diverticulum that do not contain ectopic gastric mucosa or those with rapid bleeding that prevents the accumulation of tracer in the diverticulum. False positive Meckel scans can also be caused by appendicitis, peptic ulcer, hemangioma, abscess, intussusception, Crohn's disease, small bowel lymphoma, dilated or ectopic renal collecting structures, abdominal aneurysm, Peutz-Jeghers syndrome, and intestinal duplications (2).

Depending on the presentation pattern, the differential diagnosis can include appendicitis, Crohn's disease, acute porphyria, intussusception, volvulus, small bowel obstruction, bezoar, juvenile colonic polyp, incarcerated hernia, Hirschsprung's disease, necrotizing enterocolitis, perforated viscus, gastroenteritis, Henoch-Schonlein purpura, peptic ulcer, constipation, urinary tract infection, sickle cell crisis, urolithiasis, ovarian torsion, etc. The differential diagnosis of abdominal pain alone, is extensive.

Preoperatively, hemodynamic stabilization and control over diverticular infection should be addressed when Meckel's diverticulum complications are present. Cimetidine has been used successfully to stop bleeding before diverticulectomy is performed and empiric antibiotic administration is also often indicated (7). NG tube placement can be useful in patients presenting with intestinal obstruction requiring nasogastric decompression, and it can also help rule out upper GI hemorrhage proximal to the ligament of Treitz (2).

Surgical resection is the standard treatment of choice for all patients with a symptomatic Meckel's diverticulum (7). As mentioned earlier, the morbidity associated with a Meckel's diverticulectomy precludes routine surgical resection if found incidentally. However, if the diverticulum is suspected to contain ectopic gastric mucosa, if fibrous bands extend to the umbilicus, if mesodiverticular bands are present, or if there is surrounding inflammation, surgical resection of the Meckel's diverticulum is indicated (3).

The reported surgical mortality rate for symptomatic Meckel's diverticulum patients is 2-5%. Symptomatic patients have a 10-12% incidence of early postoperative complications such as ileus, suture line or intestinal anastomotic leak, intra-abdominal abscess, and pulmonary embolism. Late postoperative complications occur in 6-8% of patients and consist of small bowel obstruction due to intestinal adhesions (12).

Questions

1. What is the most common congenital gastrointestinal anomaly?
2. What embryologic structure composes a Meckel's diverticulum?
3. Are Meckel's diverticula more likely to be found in males rather than females?
4. What kind of ectopic mucosa is commonly found inside of a Meckel's diverticulum?
5. How do Meckel's diverticula usually present?
6. How do young children with symptomatic Meckel's diverticula usually present?
7. What are the principal complications of Meckel's diverticula?

8. What is the most useful imaging modality used to diagnose a Meckel's diverticulum?
9. A false negative Meckel's scan could be due to what?
10. What is the Meckel's rule of 2's (four elements)?

Related x-rays

Meckel's Diverticulitis: Yamamoto LG. Periumbilical Abdominal Pain. In: Yamamoto LG, Inaba AS, DiMauro R. (eds). Radiology Cases In Pediatric Emergency Medicine, 1996, volume 4, case 9. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v4c09.html

Volvulus due to Meckel's: Yamamoto LG. Bowel Obstruction With Intra-Intestinal Sand. Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1996, volume 5, case 19. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v5c19.html

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Answers to questions

1. Meckel's diverticulum is the most common congenital anomaly of the gastrointestinal tract, affecting about 2% of the population.
2. The embryologic yolk-stalk or omphalomesenteric or vitelline duct
3. Meckel's diverticula appear in males and females at equal frequencies, however, males are 3 times more likely to develop symptomatic or complicated Meckel's diverticula.
4. Gastric mucosa is present in 80% of all heterotopic cases.
5. Most cases of Meckel's diverticula are asymptomatic, are detected at autopsy, or incidentally during unrelated abdominal surgery.
6. The infant or young child who has a massive, painless bout of dark red rectal bleeding most likely has Meckel's diverticulum.
7. The principal complications of Meckel's diverticulum include ulceration, hemorrhage, small bowel obstruction (may be due to volvulus or intussusception), diverticulitis, and perforation.
8. A Meckel's scan (technetium-99m pertechnetate scintigraphy).
9. False negative scans are seen in Meckel's diverticulum that do not contain ectopic gastric mucosa and in Meckel's diverticulum with rapid bleeding that prevents the accumulation of tracer in the diverticulum.
10. Meckel's rule of four 2's: a) Occurs in 2% of the population, b) Only 2% of those with a Meckel's manifest clinical problems, c) Usually located 2 feet proximal to the ileocecal valve and the diverticulum is approximately 2 inches long, d) Symptoms commonly manifest at age 2 years.

Chapter X.1. Wound Management
Jeffrey J. Wong, MD

A 7 year old male presents to the emergency department 30 minutes after sustaining a right lower leg laceration. He fell off his bicycle, causing his right lower extremity to collide with the edge of a cement park bench. This resulted in a 2 cm laceration lateral to his right shin, which started to bleed. The patient's mother firmly applied a towel to the wound to control the bleeding, and drove him to the emergency room for treatment. He denies pain in any other areas besides his wound. He denies difficulty walking or increased pain while bearing weight.

PMH is unremarkable. Immunizations are up to date.

Exam: VS are normal. He is alert and comfortable. There are no signs of trauma elsewhere. His exam is unremarkable except for his lower extremity, where he has a 2 cm vertical laceration lateral to his tibia, 6 cm inferior to the patella. The depth of the laceration is approximately 5 mm. The laceration is not actively bleeding at this time. His perfusion, sensation and motor function are intact distally. No bony tenderness or deformity is present.

The wound is infiltrated with buffered 1% lidocaine. The wound is then irrigated and explored. The laceration is closed in two layers with a 4-0 absorbable suture closure of the subcutaneous layer, followed by a 5-0 skin closure with black nylon. The nylon sutures are removed 9 days later.

Traumatic wounds are a common reason for presentation to the emergency department. A wound is defined as a physical disruption of tissue from trauma. They can be accidental as a result of trauma or intentional from surgery. Generally, wounds include abrasions, punctures, lacerations, burns and larger wounds. This chapter will focus mainly on minor abrasions and lacerations. Larger wounds, such as those requiring extensive debridement or grafts, are beyond the scope of this chapter. Burns are covered in a separate chapter.

Effective management of wounds requires a basic understanding of the physiologic process of wound healing. Wound healing can be divided into three phases: the inflammation (exudative or substrate) phase, the proliferative phase, and the remodeling (maturation) phase. The inflammation phase involves vasodilatation of capillaries in wound edges and migration of plasma, polymorphonuclear leukocytes and macrophages into the wound space. The macrophages are particularly important in removing debris and bacteria, stimulating fibroblasts, and promoting angiogenesis. The proliferative phase involves the development of granulation tissue (a new vascular and cellular tissue comprised of new capillaries, inflammatory cells, collagen, fibronectin and proteoglycans). This phase does not occur until the surface has completely epithelialized. Finally in the remodeling phase, the collagen structure becomes more organized through cross-linking and forms the appearance of a flatter, stronger scar. However, at 3 weeks, the wound has only about 40% the strength of normal tissue. At 6 to 8 weeks, the wound achieves close to 70% of its strength. Although remodeling will increase the strength of the wound for at least 2 years, the scar will never reach the strength of its original, undivided tissue.

While all wounds go through the above three phases, they do not all close in the same way. There are three distinct methods in which wounds heal and close: by primary intention, secondary intention, and tertiary intention.

In healing by primary intention, the edges of the wound are well approximated (e.g., via suturing) and allow for more rapid healing and less granulation tissue and scarring.

In secondary intention, the wound is left open with the wound edges far apart from each other. Thus, there is a greater production of granulation tissue which then must undergo contraction and epithelialization. Myofibroblasts are the cells responsible for helping the wound to contract. Epithelial cells grow from the wound edges until the wound surface is totally covered. This is a slow process; epithelialization takes place at a rate of about 1 mm/day. A clinician may intentionally allow a wound to heal by secondary intention to prevent infection in wounds in which there is significant bacterial contamination, foreign bodies, or extensive tissue trauma. By leaving the wound open, there is less chance that bacterial colonization will occur (i.e., the risk of wound infection is reduced).

Healing by tertiary intention (delayed primary closure) is intentional closure after a delay of days to weeks. Similar to secondary intention, the wound is allowed to heal open for a period of time. However, the wound is then closed once the risk of infection has decreased significantly.

Urgent problems such as active bleeding should be addressed first. Then a history should be obtained and the patient should be screened for systemic conditions that put them at risk for infection or delayed healing and wound closure. Other risk factors for infection include wounds that have been open for longer than 1 hour and contaminated wounds. Also, the history of the mechanism of injury is essential to identify wound contaminants and foreign bodies that can lead to infection or delayed closure. Depending on the degree of contamination of the wound and the patient's immunization status; cultures, antibiotics, and tetanus prophylaxis should be considered. Then, utilizing universal precautions, the wound should be examined and assessed for location, length and depth, and extent of injury. One should also look for foreign bodies, damage to nerves or tendons, and the need for debridement. A neurovascular examination is important to document before anesthesia is applied. If a fracture or foreign body is suspected, radiographs should be obtained.

The mechanism of injury is important in several specific examples. If a sharp object such as a knife or glass is responsible for a laceration over the path of a tendon, then a severed tendon or a nick in the tendon should be suspected even if the tendon function appears to be intact. Similarly, such injuries over the path of digital nerves should lead one to suspect that the digital nerve may be severed. If broken glass is responsible for a laceration, then x-rays of the wound should be strongly considered to look for glass fragment foreign bodies which are difficult to identify on wound exploration. Most glass fragments are radiopaque. Stepping on a nail which pokes through a tennis shoe puts the patient at risk of a foreign body consisting of foam rubber from the insole of the shoe once the nail is removed. Such injuries have caused wound infections and osteomyelitis due to a retained foam rubber foreign body.

Abrasions are common. An abrasion occurs when a physical force scrapes and damages superficial layers of epithelium, usually with little damage to the underlying dermis. Abrasions tend to be very simple to manage and often only require thorough cleansing of the wound. Afterwards, the wound should be dressed with ointment and a sterile bandage and kept fairly moist to prevent desiccation to allow rapid and effective epithelialization. Healed abrasions often leave the skin hyperpigmented when exposed to the sun, thus sunscreen for 6 months post-injury may be helpful to prevent hyperpigmentation.

Puncture wounds are usually caused by a sharp and pointed object and may have variable depth of penetration through the tissues. Thus, one must consider possible damage to underlying structures. Also, these wounds may contain foreign material and are ideal sites for bacteria to flourish, making infection very common. Most uncomplicated, clean puncture wounds presenting less than 6 hours after injury will only require irrigation and cleansing to remove debris and aid in visualization of the wound. These wounds can usually be dressed

with a light bandage. Irrigation under pressure is controversial since it may push foreign material and bacteria deeper into the wound. Some have recommended excision of the puncture wound (core out) for puncture wounds at high contamination risk; however, this is aggressive and unnecessary in most instances.

Antibiotic therapy in wound management is greatly dependent on the timing of administration, the mechanism of injury, the severity of the wound, and the degree of bacterial contamination. In heavily contaminated wounds, it has been shown that infection usually results despite antibiotic therapy. Thus, irrigation and debridement are more important to prevent infection by reducing the bacteria count within the wound. Also, the effect of antibiotics depends on the length of time the wound has been open. The longer the wound is exposed, the less effective antibiotics become.

For lacerations, the wound must also be cleansed. If local anesthesia is planned, then cleansing is more effectively done after local anesthesia. Several local anesthesia and wound closure options are available. Ideally, these options should be discussed with the family and a decision should be made based the medical considerations while considering patient and family preferences.

Local anesthesia will be required for most wound closures. Lidocaine is commonly used to infiltrate wounds which has a rapid onset and a duration of about 1-2 hours. Some techniques to reduce the pain associated with infiltration include buffering the lidocaine (by adding sodium bicarbonate), warming the anesthetic solution, using fine gauge needles (e.g., 30 gauge), injecting through (i.e., from inside) the wound rather than through the skin (2), and slowing the speed of injection (3). Lidocaine with epinephrine may be used under some circumstances instead of plain lidocaine. Epinephrine is a vasoconstrictor which slows the rate of lidocaine entering the general circulation, allowing a higher total dose to be given (important for large wounds), extending the duration of action, and reducing the amount of bleeding. However, vasoconstriction agents should not be used in areas with end arterioles (such as the fingers, toes, ear, penis, and the tip of the nose) to prevent ischemia and tissue necrosis (5). Flap type lacerations may also be adversely affected by epinephrine if the perfusion to this flap is marginal. Optionally, longer acting local anesthetics such as bupivacaine can be used, but many consider this drug to be more expensive with a higher risk of toxicity.

Topical anesthesia can also be used alone or as a premedication preparation for subsequent infiltrated local anesthesia. Topical anesthesia does not utilize needles and administration is relatively painless. Tetracaine-adrenaline-cocaine (TAC) gel is no longer used because the cocaine component can be absorbed by mucous membranes potentially causing seizures and death (4). Lidocaine-adrenaline-tetracaine (LAT) gel is just as effective with fewer adverse effects. LAT's major disadvantage is that it requires 30 minutes for its local anesthesia effect to take place. EMLA cream (eutectic mixture of local anesthetics) is another topical local anesthetic (6) but its onset time is similarly slow.

After local anesthesia, the wound is cleansed to help prevent bacterial infection by removing foreign bodies and reducing the bacterial count within the wound. Direct inspection and exploration of the wound is necessary to remove visible foreign bodies. Irrigation is used to reduce surface bacterial counts and to rinse microdebris from the wound. Although many irrigation fluids have been studied, sterile normal saline is inexpensive and effective. Concentrated povidone-iodine, hydrogen peroxide, and detergents can cause significant tissue toxicity and are not recommended for internal wound irrigation (7). These agents are more effective on intact skin and possibly abrasions. Thus, povidone-iodine can be used to sterilize the skin as a skin prep for suture closure, but the wound should be irrigated with saline and not with povidone-iodine.

Sutures are the most common method of wound closure for lacerations. They have the greatest tensile strength and the lowest rate of dehiscence. However, one must consider the requirement of local anesthesia and sometimes sedation, cost issues (sutures are inexpensive, but they require a set of instruments and often, suture removal at a follow up visit), and more time and skill to apply.

Non-absorbable sutures made of nylon or polypropylene are commonly used for closing the skin layer of a laceration. Advantages include their ability to retain tensile strength for more than 60 days, and their relatively low tissue reactivity. These sutures require a follow-up visit for suture removal. In contrast, absorbable sutures such as chromic gut and polyglactin do not need to be removed. They are typically used for deeper layers or for subcuticular tissues. Deep sutures are beneficial in reducing the skin tension required for the skin sutures and the prevention of hematomas, dead space, and scarring. Some physicians prefer to use special fast absorbing sutures in the outer skin layers to avoid the pain and anxiety associated with suture removal (5) (popular products include fast absorbing gut and Vicryl Rapide). Otherwise, sutures should be removed after about 3-14 days depending on their location: face (3-5 days), scalp (5-7 days), trunk (7-10 days), extremities (10-14 days). Facial sutures should be removed earlier to prevent the formation of sinus tracts. After suture removal, wound closure tape is usually applied to reinforce the wound and prevent dehiscence.

The advantages of wound closure tape are that there is almost no tissue reactivity and they can be applied very rapidly. However, they are not able to evert the wound edges or close deep tissue. Tape should not be used alone in areas of high tension since they have low tensile strength and a high rate of dehiscence. Wound closure tape would be acceptable for smaller lacerations which are under little or no tension.

Tissue adhesives, which are cyanoacrylates, have been found to have negligible tissue toxicity, bacteriostatic properties, and good tensile strength (7). Histoacryl Blue (HAB or N-butyl-2-cyanoacrylate) has been in use for the past 20 years in Europe and Canada, but it is not approved for use in the U.S. (9). 2-octylcyanoacrylate (2-OCA, Dermabond trade name) was approved for use in the U.S. in 1998. After holding the two edges together, it is applied to the surface of the skin, requiring about 30 seconds for polymerization, forming a strong bond to the uppermost layer of the skin (10). This polymer holds the edges of the laceration together, allowing for good wound approximation and healing. The adhesive should never be placed inside the wound, since this results in a foreign body effect and impedes the wound edges from approximating. Aside from increased flexibility, 2-OCA has been found to be 3 to 4 times stronger than HAB, allowing it to be used on larger lacerations and incisions (11). 2-OCA can be used on almost any size laceration with an intact epidermis, although subcutaneous sutures are recommended on lacerations to extremities (7). This is due to the high tissue tension in these areas. For deeper lacerations to the epidermis, absorbable sutures can be used in the deep tissues in conjunction with tissue adhesive applied to the surface edges of the wound. After about 7-10 days, 2-OCA peels off, avoiding the need for the patient to return for suture removal. However, water can disrupt the 2-OCA bonds and cause premature peeling off of the adhesive. Thus, children should be encouraged to keep the affected area dry. Some of the other advantages of 2-OCA over sutures include ease of application, quicker application time (less than half the time needed for sutures), and fewer cases requiring local anesthesia (10). Tissue adhesives have been found to have comparable cosmetic results when compared with sutures (3,4,12). Some disadvantages include less tensile strength compared to sutures, and increased wound dehiscence over joints and high-tension areas. Tissue adhesives are seemingly simple, but they should be used by experienced personnel since they have many adverse effects described which are preventable if used in the correct manner, and if their use is avoided in wound conditions which are unsuitable for tissue adhesives (e.g., highly mobile areas and on the feet).

Questions

1. What is the purpose of using epinephrine in local infiltration and topical anesthesia?
2. Name the drawbacks of tissue adhesives in laceration repair.
3. What has the best cosmetic result in the repair of lacerations: sutures or tissue adhesives?
4. How long does it take for the tissue adhesive 2-OCA to fall off after application?
5. What are the adverse effects of using tetracaine adrenaline cocaine (TAC) gel?
6. What is the major clinical reason for preferring healing by secondary or tertiary intention (as opposed to primary closure)?
7. True/False: Antibiotics have only a modest effect on reducing the rate of wound infections in contaminated wounds.

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Answers to questions

1. Since epinephrine is a vasoconstrictor, it slows the rate of local anesthetic release into the general circulation permitting a higher total dose of local anesthetic that can be given (useful if the wound is large), it extends the duration of action, and decreases bleeding.
2. Lower tensile strength compared to sutures and thus it can't be used in areas of high tension such as wounds over joints. If it gets wet, the adhesive may fall off prematurely.
3. The research done on the comparisons between sutures and tissue adhesives have shown that they have comparable cosmetic results.
4. Approximately 7 to 10 days
5. Cocaine component: arrhythmia, urticaria, drowsiness, excitation, seizure, vomiting, flushing, and death. TAC should be avoided near mucous membranes. TAC is no longer available in most centers.
6. Significantly contaminated wounds, are at greater risk of infection if closed by primary intention.
7. True. Heavily contaminated wounds will develop infection despite antibiotic treatment.

Chapter X.2. Inguinal Hernias and Hydroceles
Leticia P. Borja, MD

A 2 week old male infant, born at 38 weeks gestational age, presents for his first visit to a pediatric clinic. According to his parents, he has been doing well since birth. Their only concern is the persistence of a bulge in his right scrotum. On review of birth records, a moderate-sized scrotal mass had been appreciated on newborn examination with no other abnormalities noted. According to his parents, the bulge has not changed in size since birth and there has been no noticeable discomfort.

On exam, a moderate sized right scrotal mass is palpated. It is firm, smooth, non-fluctuant and non-tender. It brilliantly transilluminates. There is no reduction with compression of the mass. Both testes are descended. No inguinal or abdominal masses are appreciated on palpation. A diagnosis of non-communicating hydrocele is made. His parents are reassured and counseled on the possibility of a communicating hydrocele/complete inguinal hernia and to proceed to an emergency room if signs or symptoms of incarceration and strangulation occur. On subsequent well child visits, the right scrotal mass is noted to minimally decrease in size. His parents continue to report no fluctuation in size during activity, crying or defecation. At his 12 month well child visit, the right scrotal mass is noted to be unchanged since his last visit 3 months prior. He is referred to a pediatric general surgeon for evaluation. Elective surgical correction is performed.

Inguinal-scrotal swelling is a common finding in the pediatric population. Of the possible causes, the most common diagnoses are hernias and hydroceles. Approximately 1-2% of male newborns have a hydrocele. Most are non-communicating hydroceles (1). The estimated incidence of inguinal hernias in children is 5-50/1,000 live births. It is seen more frequently in males than females with a ratio of about 5:1 with a definite familial tendency. About 50% of cases present before 12 months of age with most occurring in the first 6 months of life. Approximately 99% of all inguinal hernias in children are indirect inguinal hernias. Direct hernias are rare. Most inguinal hernias are unilateral with about 60% occurring on the right side and 30% on the left side. Ten percent are bilateral (i.e., clinically apparent at initial presentation). Of note, inguinal hernias are more common in premature infants with an incidence of 5-30%. Most cases are bilateral, occurring in about 62% of affected premature infants (2-5).

Normally, in the male fetus, the testes descend to the vicinity of the internal ring of the inguinal canal by approximately 28 weeks gestational age. Then, by about 29 weeks gestation, the testes descend into the scrotum. With testicular descent, the lining of the peritoneal cavity extends into the inguinal canal and scrotum. This peritoneal canal is referred to as the processus vaginalis. Each testis descends through the inguinal canal external to the processus vaginalis. In the female fetus, a similar mechanism with descent of the ovaries into the pelvis occurs. The processus vaginalis in females extends through the inguinal canal into the labia majoris and is referred to as the canal of Nuck (2). In males, a hydrocele is formed when there is patency of the processus vaginalis between the scrotum and the peritoneal cavity resulting in an accumulation of fluid between the layers of the tunica vaginalis surrounding the testis. In the weeks prior to birth or shortly after, the processus vaginalis closes spontaneously in the area of the internal ring, obliterating the entrance to the inguinal canal. The scrotal fluid collection that remains within the tunica vaginalis is referred to as a scrotal hydrocele, or a non-communicating hydrocele. If the processus vaginalis fuses proximally and distally but remains open in between, the isolated fluid collection is referred to as a hydrocele of the cord. This type of hydrocele, although not in communication with the peritoneal cavity or the scrotum, is often associated with a hernia and/or a scrotal hydrocele (6). In some older boys, a scrotal hydrocele may result from inflammation within the scrotum caused by various conditions including testicular torsion, torsion of the appendages, epididymitis, and testicular cancer (1,4). When the processus vaginalis fuses distally but remains patent proximally, abdominal contents can enter the inguinal canal resulting in an inguinal hernia. However, if the processus vaginalis fails to fuse completely, there will be communication between the scrotum and the peritoneal cavity through the patent processus vaginalis resulting in an inguinal-scrotal hydrocele, or communicating hydrocele. Of note, there is a rare but important type of communicating hydrocele called an abdominal-scrotal hydrocele. With this type of hydrocele, the communication is between the scrotum and a cystic loculation of fluid within the lower abdomen. This may result in recurrent communicating hydroceles or unusually large hydroceles. If a communicating hydrocele is large enough, abdominal contents may extend through the patent processus vaginalis to the scrotum resulting in an inguinal-scrotal hernia (complete inguinal hernia). A similar mechanism may result in hernias in girls. The hernia sac in males and females may contain intestine or omentum, with the ileum being the most common intestinal component. However, other possible intestinal components include colon, appendix, and Meckel's diverticulum (hernia of Littre). In males with undescended testes, a testis may be contained within a hernia sac. In females, a hernia sac may contain an ovary, fallopian tube, or both (6). Of note, it is possible for a testis to be found in the hernia sac of a female infant if testicular feminization (complete androgen insensitivity) is present. More than half of patients with testicular feminization have an inguinal hernia (4).

In differentiating a hydrocele from a hernia, history and physical examination can be diagnostic. The most important information elicited from parents is a history of fluctuation in the volume of the mass that would be consistent with a hernia or communicating hydrocele. Parents may report an increase in size that is particularly noticeable at times of increased intra-abdominal pressure (activity, crying or straining). At rest, the bulge will be noted to spontaneously decrease in size. Parents may also report previous reduction of the mass by either themselves or another physician. A history of fussiness, obvious discomfort, poor feeding, vomiting, and abdominal distention would suggest incarceration. The physical examination starts with the child supine. The child should be positioned with legs extended and arms raised over the head. This usually results in crying, thereby causing an increase in intra-abdominal pressure. The mass is palpated and evaluated for tenderness, tenseness, and associated skin discoloration that, if present, would suggest incarceration and possible strangulation. This would be an indication for immediate referral to a pediatric surgeon. If the mass is non-tender, smooth, firm and located in the scrotum, a hydrocele is likely to be present. Of note, a hydrocele may also be found in the spermatic cord. A scrotal hydrocele should be moved away from the inguinal canal and palpation of normal cord structures superiorly should be performed to exclude the presence of a hernia. The testes may not be palpable. If a patient presents with a large hydrocele or a history of recurrent communicating hydroceles with or without a palpable ipsilateral lower abdominal mass, an abdominal-scrotal hydrocele should be suspected. If compression of the fluid-filled mass completely reduces the size of the hydrocele, a communicating hydrocele or hernia is the likely diagnosis. An inguinal hernia is non-tender, soft, reducible and can be located in the inguinal canal or may extend into the scrotum (inguinal-scrotal hernia). Of note, retractile testes, a common finding in infants and young children, can resemble an inguinal hernia. To avoid misdiagnosis, palpation of the testes should be done prior to palpation of an inguinal mass. The physical examination continues with the child erect. This raises the intra-abdominal pressure. Any fluctuation in the size of the mass should be noted. If the

child can cooperate, cough and Valsalva maneuvers (e.g., attempts to blow into an obstructed straw or a balloon) should be encouraged. An increase in size of the mass would be consistent with a hernia or communicating hydrocele.

Transillumination of the mass can be attempted. A hydrocele will brilliantly transilluminate. However, in children, inguinal-scrotal hernias and incarcerated bowel may also brilliantly transilluminate. Thus, transillumination in the pediatric setting may be unreliable. The internal ring of the uninvolved side should be examined before proceeding to the internal ring of the affected side. If an inguinal hernia is present, abdominal contents may be palpated extending through the internal ring (2,3,6).

If there is a history suspicious for a hernia but no mass can be demonstrated on examination, it may be helpful to empty the bladder which, when full, can block the internal inguinal ring and mask an inguinal hernia. Otherwise, a classic history of intermittent inguinal, scrotal or labial swelling that spontaneously reduces may be all that is necessary for diagnosis. However, another physical examination finding that can be present with inguinal hernias is a thickened spermatic cord with an associated "silk" sign. The spermatic cord is palpated over the pubic tubercle and a "silky sensation" is appreciated when the two layers of peritoneum are rubbed together. This finding, along with a history of a hernia, is highly suggestive of an inguinal hernia (2).

A scrotal hydrocele that is sufficiently large and tense may cause ischemic injury to the testis. A communicating hydrocele may enlarge and lead to development of an inguinal-scrotal hernia (6). Nine to twenty percent of inguinal hernias in children become incarcerated with more than half of those cases occurring in children less than 12 months of age. The incidence of incarceration increases in premature infants and in term female infants (2,5). When incarcerated, complete manual reduction of the hernia may not be possible. Strangulation of the hernia can occur and ischemic injury to intestine and testis/ovary may result (3,6). Intestinal obstruction, intestinal gangrene, and gonadal infarction occur more commonly in the first 6 months of life (4). Thus, because the risk of incarceration is high, particularly in infants, with a risk of strangulation, prompt surgical intervention is recommended as soon as the diagnosis is made.

The differential diagnosis of inguinal-scrotal swelling in children (6,7) can be classified based on acuteness of presentation, tenderness, location (intratesticular versus extratesticular), and transillumination. All hydroceles are non-acute, non-tender and they transilluminate. They are extratesticular, but scrotal hydroceles may be difficult to distinguish from an enlarged testicle on palpation. Communicating hydroceles are compressible (that is, they decrease in size with pressure), while non-communicating hydroceles will not change in size.

Inguinals hernias are usually non-acute and non-tender. They usually do not transilluminate. Incarcerated inguinal hernias are usually acute and tender. Vomiting may be present. Non-communicating hydroceles are frequently mistaken for incarcerated hernias, because they do not change in size with compression (seemingly non-reducible). However, scrotal hydroceles are spherical or oval in shape, while an incarcerated inguinal hernia is usually tubular in shape (often shaped like a small banana with a slightly tapered point at the end). Additionally, hydroceles are usually softer in consistency, while incarcerated hernias are the consistency of a refrigerated hot dog and sometimes harder than this. A hydrocele of the cord can be very difficult to distinguish from an incarcerated hernia, but this should be suspected if the onset is non-acute, it is non-tender, and the child's behavior appears to be normal.

Other diagnoses in the differential include lymph nodes, undescended or retracted testis (smaller in size), varicocele (soft spaghetti or bag of worms consistency), and spermatocele. Other considerations include epididymal cyst, testicular cancer, peritesticular rhabdomyosarcoma, benign soft tissue tumors, meconium sequestration, testicular torsion (tender), torsion of appendages, epididymitis, trauma, idiopathic scrotal edema, and Henoch-Schonlein purpura.

If there is uncertainty in the diagnosis, an ultrasound examination may aid in differentiating a hydrocele from a hernia, may confirm the presence of an abdominal-scrotal hydrocele, or may rule out other causes of inguinal-scrotal swelling. In a female, ultrasound examination can be used as part of the evaluation for testicular feminization (4). It can also be used to examine both ovaries when an incarcerated ovary is suspected (6). Abdominal x-rays are unnecessary for diagnosis of an incarcerated hernia, although they may be helpful in confirming an intestinal obstruction. If an incarcerated or strangulated hernia is associated with bowel obstruction or shock, laboratory studies and vascular access are indicated (5).

Treatment is usually not required for uncomplicated, simple hydroceles (non-communicating) because they tend to decrease in size with complete resolution in the first 2 years of life. Significant hydroceles persisting beyond 12-24 months are likely to be communicating and are generally surgically corrected at that time (1). However, early surgical repair is recommended for large, tense hydroceles because they rarely disappear spontaneously, they can cause ischemic injury to the testis, and they may be difficult to distinguish from hernias. Communicating hydroceles also require early surgical repair due to the fact that they may progress to symptomatic inguinal-scrotal hernias (6). All inguinal hernias will eventually require surgery. In fact, inguinal hernia repair is the most common surgical procedure in children (4). However, the urgency of surgical correction varies. In an outpatient setting, if a child presents with an inguinal hernia but is otherwise well (no obstruction or shock), manual reduction should be attempted. About 95% of inguinal hernias can be reduced by applying gentle but steady upward pressure on the hernia sac. If the hernia is easily reducible, referral to a pediatric surgeon should be done for elective surgical repair. While awaiting repair, parents should be counseled to seek immediate evaluation and treatment in an emergency department if signs and symptoms of incarceration and strangulation occur. Inguinal hernias that cannot be easily reduced are incarcerated and require immediate referral to an emergency department. In an emergency department, manual reduction can be attempted with sedation. Once the child is sedated, firm steady upward pressure can be applied to the hernia sac using one hand while the other hand gently guides the neck of the hernia sac into the distal ring of the inguinal canal. A Trendelenburg position may be helpful. If reduction is successful, a pediatric surgeon should be consulted for outpatient follow-up. However, children with difficult to reduce hernias or a history of incarceration in the past are at high risk for future incarceration and strangulation and should be managed more urgently. Some cases require inpatient observation. If reduction is unsuccessful, then a pediatric surgeon must be consulted immediately. If, however, a child presents with an incarcerated inguinal hernia and symptoms of intestinal obstruction or shock, a pediatric surgeon must be consulted emergently while resuscitation begins with intravenous fluids and nasogastric tube decompression of the stomach (5).

In young females, an ovary may incarcerate in the hernia sac. This has a spherical shape and the child is often asymptomatic with the exception of the inguinal mass. While incarcerated bowel is at risk for ischemia and must be surgically corrected immediately, the vascular supply to the incarcerated ovary is usually not compromised, thus, this is often less emergent.

Elective surgical repair can be safely done as an outpatient. Hospitalization may be necessary for children at high risk for post-operative/post-anesthesia complications (e.g., premature infants <60 weeks of post-conception age and infants with chronic medical conditions including heart disease, respiratory disease and seizure disorder) (2). Surgical correction is done through an inguinal incision. The spermatic cord is identified and, if present, a hydrocele is excised. If a hernia is present, reduction is performed. In the case of an incarcerated hernia, careful inspection of the incarcerated bowel is done to assess viability. After inspection and reduction, a high ligation of the processus vaginalis is performed (1,4). Of note, females undergoing surgical correction of a hernia should be evaluated for the possibility of testicular feminization. A rectal examination should be done to palpate the uterus. If a uterus is not palpable beneath the

symphysis pubis in the midline, a pelvic ultrasound examination should be done to evaluate for normal female anatomy. If the results are inconclusive, the hernia sac must be explored during surgery and the presence of a fallopian tube verified. If present, testicular feminization can be ruled out. Conversely, the presence of testes confirms the diagnosis. If neither fallopian tube nor testis is found, an endoscopic examination of the vagina after surgery should be performed to evaluate for a cervix. If a cervix is present, testicular feminization can be ruled out. However, if it is absent, chromosomal analysis will need to be done (2,6).

There is controversy surrounding the topic of contralateral surgical exploration at the time of herniorrhaphy. Studies have shown that development of a contralateral inguinal hernia after unilateral herniorrhaphy occurs with an incidence of 12-30% (>10% since the contralateral hernia often develops later). Bilaterality is more frequent in females, children less than 12 months of age, and children with left-sided inguinal hernias. For this reason, it is recommended that bilateral surgical exploration be done in males less than 12 months of age, females less than 24 months of age, and children at high risk for development of inguinal hernias. Bilateral surgical exploration should also be strongly considered in children less than 24 months of age with left-sided inguinal hernias. Of note, contralateral exploration can be avoided with laparoscopic herniorrhaphy. This technique allows for visualization of the contralateral side during repair of the affected side. However, the surgeon must be experienced in laparoscopic technique. In general, the decision to undergo bilateral surgical exploration should be based on surgical expertise and a child's pre-operative medical condition (2).

Premature infants will often develop a symptomatic hernia while remaining hospitalized for prematurity. These infants should have surgical correction of the hernia prior to discharge from the hospital. Other significant risk factors for development of an inguinal hernia include presence of a ventriculoperitoneal shunt or peritoneal dialysis catheter. These devices cause increased intra-abdominal pressure resulting in a high incidence of inguinal hernias in affected infants. They are also associated with greater risk for surgical complications. It is recommended that prophylactic antibiotic therapy with ampicillin and gentamicin be given perioperatively to children with ventriculoperitoneal shunts. This is also the recommendation for children with congenital heart disease. Other conditions associated with an increased incidence of inguinal hernias include congenital dislocation of the hip, ascites, congenital abdominal wall defects, meconium peritonitis, connective tissue disorders (Ehlers-Danlos syndrome), mucopolysaccharidosis (Hunter-Hurler syndrome), ambiguous genitalia, hypospadias/epispadias, cryptorchid testes, and cystic fibrosis. Cystic fibrosis is also associated with agenesis of the vas deferens. Thus, if bilateral absence of the vas deferens is noted incidentally during herniorrhaphy in a child without a prior diagnosis of cystic fibrosis, an evaluation for cystic fibrosis should be done including a sweat chloride test and/or DNA testing. However, agenesis of the vas deferens can also be an isolated finding. If a child has cryptorchid testes and an inguinal hernia, elective orchiopexy should be done along with herniorrhaphy to reduce the risk for ischemia and infarction or the testis (2,4).

Most hydroceles resolve by 12-24 months of age following reabsorption of the hydrocele fluid. However, if the hydrocele persists beyond this time frame, if it is large and tense, or if the hydrocele is communicating, it is unlikely to resolve spontaneously and can be difficult to distinguish from a hernia. In these cases, as with hernias, surgery can be curative. However, there can be complications of surgery including damage to intestine, testis and vas deferens or to ovary and fallopian tube. Rarely, the bladder may be damaged with resultant urinary ascites. A surgeon should be able to recognize and appropriately manage such injuries (6). Post-operative complications including wound infection and hernia recurrence are uncommon. In fact, the hernia recurrence rate is less than 1% (2). More commonly, a recurrent swelling is due to reaccumulation within the tunica vaginalis and/or enlargement of retained tunica vaginalis tissue due to edema. These will often resolve spontaneously without the need for reoperation (6). However, there is an increased risk for hernia recurrence after repair of incarcerated or strangulated hernias as compared to elective surgical repair (4). Children with connective tissue disorders, chronic respiratory disease, and chronic illnesses associated with increased intra-abdominal pressure are also at higher risk for hernia recurrence (2).

Questions

1. True/False: Bilateral inguinal hernias are common in premature infants.

2. Which of the following statements is false?
    a. Each testis descends through the inguinal canal into the scrotum within the processus vaginalis.
    b. A hydrocele can result from incomplete fusion of the processus vaginalis.
    c. A scrotal hydrocele, or simple hydrocele, is a type of non-communicating hydrocele.
    d. A communicating hydrocele can develop into an inguinal-scrotal hernia. Some use the terms interchangeably.
    e. A hernia sac can contain intestine, omentum, testis/ovary or fallopian tube.

3. What is the classic clinical presentation of an inguinal hernia?

4. True/False: The risk of incarceration and strangulation of an inguinal hernia is highest in the first 12 months of life.

5. Which of the following is not part of the differential diagnosis of an inguinal-scrotal swelling in children?
    a. Varicocele
    b. Undescended or retracted testis
    c. Volvulus
    d. Testicular torsion
    e. Testicular cancer

6. True/False: All inguinal hernias will eventually require surgery.

7. Which of the following is not a risk factor for development of an inguinal hernia?
    a. Presence of a ventriculoperitoneal shunt
    b. Congenital heart disease
    c. Prematurity
    d. Cystic fibrosis
    e. Family history of inguinal hernias

8. True/False: After herniorrhaphy, hernia recurrence is rare.

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Answers to questions

1. True
2. a
3. Intermittent inguinal, scrotal or labial swelling that spontaneously resolves.
4. True
5. c
6. True
7. b
8. True

Chapter X.3. Appendicitis
Walton K.T. Shim, MD

A 7 year old girl presents to the emergency department with a chief complaint of abdominal pain for one day. Mid-abdominal pain started after lunch yesterday. This was followed by vomiting her lunch and a bowel movement, which did not relieve the pain. She did not feel like eating dinner and went to bed but slept fitfully. By morning the pain had increased and she vomited again. The pain has moved to the right lower quadrant and is increased by walking and coughing.

ROS: Non-contributory. No dysuria, cough or URI. No similar GI problem in the family. Pain remained constant in RLQ without radiation.

Exam: T 37.1, R 16, P 100, BP 150/70. She is alert, but subdued. HEENT Negative. Neck is supple. Chest is clear. Heart regular without murmur. Abdomen: Bowel sounds hypoactive with right lower quadrant tenderness and guarding. No organs or masses are felt. Right lower quadrant rebound tenderness is present. Genitalia: Normal; no hernias. Rectal: No masses or tenderness. She walks slowly and slightly hunched.

Lab: CBC WBC 14.0, 60% Segs, 15% Bands. UA 10-15 WBC, 15-20 RBC, no bacteria. Abdominal radiographs: Non-specific, no fecalith is seen.

Impression: Acute appendicitis

Surgery: Acute appendicitis; appendectomy performed

Pathology of appendix: Acute appendicitis

The recorded history of appendicitis demonstrates the evolution of our understanding and treatment of a disease process. It starts in the early 18th century and is summarized by Dr. Mark Ravitch in the chapter titled "Appendicitis" of the text Pediatric Surgery. It is recommended to all students of medicine (1). The Pathologist Reginald Fitz of Boston first described the condition of appendicitis in 1886 and in 1887, the Philadelphia surgeon T.G. Morton performed the first successful removal of an appendix which had been perforated. Charles McBurney immortalized "McBurney's point" when he described it in 1889 as the point of greatest tenderness located 1.5 to 2 inches (4 to 5 cm) from the anterior spine of the ileum on a line drawn between that point and the umbilicus.

It is estimated that 60,000 - 80,000 children are diagnosed with appendicitis annually (2), making it the most frequently performed emergency medical procedure in childhood. About 100 will die from complications (0.2%).

Obstruction of the lumen by impacted fecal material is the prime cause of appendicitis. This creates an increase in intraluminal pressure, edema and ultimately mucosal ulceration leading to infection and perforation. Obstruction from bacterial infections such as Yersinia, Shigella and Salmonella, from systemic viral infections, and from parasitic ascaris are rare causes. The earliest cases recorded were caused by ingested foreign bodies.

The diagnosis of acute appendicitis is a good example of critical thinking in medicine. It involves both inductive and deductive reasoning. It starts with a chief complaint, or the reason the patient comes to see the physician, followed by a probing evaluation and expansion of the chief complaint into what amounts to a history of symptoms surrounding the chief complaint or the present illness. We apply the recent mnemonic of S.O.A.P. (Subjective, Objective, Assessment, Plan) to the diagnosis and treatment of appendicitis.

S (subjective or symptoms): We find the subjective symptom of abdominal pain to be epigastric or mid-abdominal in location associated with anorexia and vomiting in most cases. This corresponds to the period of early obstruction and edema of the appendiceal lumen. This colic of the appendix, as with obstructive colicky pain of the entire intestinal tract is appreciated in the mid-abdomen or epigastrium. As the process of obstruction proceeds to edema and inflammation of the appendiceal wall and serosa, pain starts to localize in the dermatome overlying the infected appendix which is usually in the right lower quadrant. With a knowledge of pathophysiologic progression of the disease the physician/diagnostician/sleuth can round out the symptomatology with probative questions to elicit

predictable symptoms associated with bowel inflammation such as the presence of an urge to defecate during the obstructive phase caused by the attempt of the intestine/appendix to expel the offending impacted material, anorexia and/or vomiting, pain with walking, and sudden pain relief with rupture only to have more intense symptoms recur as peritonitis becomes established.

At this point with the knowledge that abdominal pain can also be caused by genitourinary, respiratory, gynecological, lymphatic and neurological diseases, application of deductive reasoning should lead the diagnostician to ask whether or not the child has a respiratory infection with cough, sore throat or chest pain; whether or not there is radiation around the right flank or dysuria and groin pain indicating a urological cause; or in a girl, whether or not the pain radiates to the anterior right thigh indicating pain of ovarian origin. In post menarchal females, low abdominal pain occurring in mid-cycle may be caused by a ruptured ovarian follicle which is called mittelschmerz (literally, middle pain). Infected lesions of the right lower extremity may cause acute femoral and/or iliac adenitis and tenderness. Neurological causes such as nerve root pain should also be considered. Having eliminated these, concentrates the symptoms in the gastrointestinal tract. To rule out small bowel pathology, such as acute gastroenteritis, flu syndrome, Henoch-Schonlein purpura, chronic GI problems, the investigator must question the chronicity of the symptoms (regional ileitis), the involvement of family members (acute gastroenteritis), the presence of blood in the stools (intussusception and intestinal infection), etc. Once these are eliminated and the general health of the child has been established, the diagnostician can move on to the next phase which is observation.

O (objective or observations): It is of interest that colicky pain caused by obstruction of a hollow viscus is somewhat ameliorated by movement on writhing, whereas peritoneal pain is aggravated by movement. So we see that children with appendiceal inflammation causing peritoneal irritation tend to lie motionless and often say that the pain is aggravated by walking.

The next step in physical diagnosis and slightly more intrusive is auscultation with a stethoscope. As appendiceal inflammation progresses, the protective mechanism of the bowel causes it to become less active and bowel sounds are diminished until the belly becomes quiet with frank peritonitis. Normal or hyperactive bowel sounds should cast doubt on a diagnosis of appendicitis. While the examiner is evaluating bowel sounds, he or she should listen to the lower lobes of the chest as pneumonia of the lower lobes can cause inflammation of the lower thoracic dermatomes and be interpreted as abdominal pain.

Peritoneal pain can and should be elicited by palpation which should start in the LLQ and progress counterclockwise ending in the RLQ. If the examiner starts in the area of pain first, the child will start crying and make further evaluation difficult. The stiffening of the abdominal muscles to restrict deeper palpation is called voluntary guarding and is an important observation when limited to the RLQ. Further inflammation of the serosal surface leads to involuntary guarding or spasm indicating peritonitis.

Finally the physical examination portion of observation should conclude with an evaluation of groin tenderness to rule out a hernia or iliac adenitis as the cause for abdominal pain. A rectal examination may also be indicated in appendiceal perforation when a pelvic abscess is suspected.

A (assessment): Acute appendicitis is the most likely explanation for the findings since the patient's temperature is usually not elevated but the WBC is frequently slightly increased. There may be a left shift of the white count with bands being elevated even though the WBC is normal. The microscopic blood and white cells in the urine can be explained by an inflamed appendix overlying the right ureter causing transmural inflammation with blood and white cells in the urinalysis. This assessment is strengthened by the absence of dysuria and pain distribution in the area usually manifested in renal colic (right flank and groin).

The single most important observation which places acute appendicitis at the head of a list of differential diagnoses is RIGHT LOWER QUADRANT tenderness. Tenderness should be <u>persistent</u> and <u>constant</u>. Inconsistent tenderness casts doubt on the diagnosis of appendicitis. In addition to the laboratory tests of CBC with differential and a urinalysis I usually obtain an abdominal series looking especially for a RLQ fecalith, air/fluid levels, abnormal quantities of stool and signs of bowel obstruction and/or masses.

The CT scan should be used judiciously in cases when a diagnosis of appendicitis cannot definitely be made or ruled out. It is probably the single most important recent addition to the physician's armamentarium of diagnostic tools, but should not be used in place of a thorough history of symptoms and a good physical examination.

A repeat abdominal examination following an enema when much stool is present on rectal examination or abdominal radiographs may clarify the diagnostic dilemma. It is important to remember that initial symptoms frequently ameliorate with time.

P (plan): When the assessment leads to a diagnosis of acute appendicitis, immediate appendectomy should be scheduled. If perforation is suspected because of the severity of symptoms and the presence of peritonitis or evidence of perforation on CT scan, preoperative antibiotics should be administered and continued post-operatively.

Since these children have not eaten for a day or so and probably have vomited, dehydration and contraction of the extracellular space is an important consideration. Proper and adequate intravenous fluid administration should be given. If dehydration is severe and peritonitis is present, the bladder must be catheterized to monitor urine output as a reflection of adequacy of fluid administration. It is not unusual that three or four times the maintenance rate of electrolyte rich fluid is required for extracellular repletion and adequate blood volume support. Those patients with peritonitis should have particular encouragement to cough and deep breathe to prevent atelectasis and pneumonia as abdominal pain and distention cause elevation and splinting of the diaphragm leading to inadequate lung expansion and retention of secretions.

Questions

1. What is the difference between colicky and peritoneal pain?
2. Where is McBurney's point?
3. What two characteristics of the tenderness at McBurney's point make the diagnosis of appendicitis?
4. In cases of right lower quadrant pain and tenderness what is the second most frequent system implicated as its cause?
5. What is mittelschmerz?

Related x-rays

Ruptured appendix case: Yamamoto LG. Abdominal Pain and the Peritoneal Fat Margins. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1995, volume 3, case 19. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v3c19.html

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Answers to questions
1. Movement alleviates colicky pain but exacerbates peritoneal pain.
2. 4 to 5 cm (1.5 to 2 inches) cephalad on a line drawn between the anterior-superior iliac spine and the umbilicus.
3. Persistent and constant in nature.
4. Genitourinary.
5. Literally "middle pain" caused by a ruptured ovarian follicle which occurs approximately in mid-menstrual cycle.

Chapter X.4. Intussusception
Lynette L. Young, MD

An 18 month old male presents to the emergency department with six hours of stomach pain. He awoke at 0400 crying. His mother carried him and he settled down after a few minutes and then fell back asleep. Over the next few hours, he woke up intermittently crying. His appetite has been poor since the onset of these symptoms. He is able to walk but prefers to be carried by his mom this morning. He is less playful than usual. He would sometimes bend down crying. There is no vomiting or diarrhea. His last stool yesterday was normal. There is no fever, cough, or runny nose. There is no history of abdominal trauma.

Exam: VS T37.6, P 118, R 24, BP 85/55, weight 11kg. He is awake, alert, and being carried by mom. His skin is pink with good perfusion and brisk capillary refill. His oral mucosa is pink and moist. There are no ulcers in the posterior pharynx. His tympanic membranes are normal. Heart regular rhythm and normal rate. Lungs are clear with good aeration. His abdomen is soft and not distended, with normoactive bowel sounds, and no masses noted. It is difficult to determine if any abdominal tenderness is present. His genitalia are normal (no scrotal/testicular swelling or tenderness). His distal extremities are warm and the distal pulses are strong. He is responding to mom appropriately.

An abdominal series reveals a soft tissue density in the right lower quadrant. Intussusception is suspected. A water-soluble contrast enema is performed. An intussusception is identified at the hepatic flexure. The ileocolic intussusception is successfully reduced. There was reflux of the contrast into the ileum. Admission to the hospital is discussed with the mother, but she refuses. He is observed in the emergency department. After a short nap, he is able to tolerate oral fluids and his behavior normalizes. The risk of recurrence is discussed with his mother. His pediatrician is contacted and the patient is then discharged home.

Intussusception is a common abdominal emergency in children. Intussusception is best described as a portion of the intestine which telescopes into a more distal intestinal segment. It is one of the most common causes of abdominal obstruction in infants. Intussusception occurs most often in patients between 3 to 12 months of age. There is a male to female predominance of 2:1. It is often difficult to diagnose because of the variable presentation of symptoms in a young infant.

The most common type of intussusception is ileocolic (also known as ileocecal) (90%). A portion of terminal ileum intussuscepts through the ileocecal valve into the colon. The intussusception may sometimes extend all the way to the rectum. Other types of intussusception that are rarer include ileoileal, colocolic, and ileoileocolic. The majority of intussusceptions are idiopathic. An anatomic lead point (a piece of intestinal tissue which protrudes into the bowel lumen such as a polyp) occurs in approximately 10% of intussusceptions. This is most often found in children older than 2 years. Possible lead points include Meckel's diverticulum (most common), polyps, an inflamed appendix, neoplasm (lymphoma), and ileal duplications. Intussusceptions with lead points are more common in patients with Henoch-Schonlein purpura (intestinal wall hematoma) and cystic fibrosis (hypertrophied mucosal glands). In infants it is hypothesized that hypertrophied Peyer's patches, following a respiratory infection or gastroenteritis, may serve as the lead point.

The mesentery is pulled along with the intussusceptum (leading invaginating segment) into the intussuscipiens (receiving segment). The intussusceptum is propelled distally through peristalsis. The mesenteric vessels are compressed leading to venous obstruction. The intussusceptum becomes engorged causing bleeding from the mucosa (bloody mucusy stools, sometimes known as currant jelly stool since extreme amounts of blood in the stool will loosely resemble the red jelly of currant berries). However, it should be noted that any blood in the stool may be caused by an intussusception. With a prolonged intussusception, perfusion to the intestine may be compromised, which can then lead to bowel necrosis, perforation, and shock.

The classic triad of intussusception include crampy (intermittent, also known as colicky) abdominal pain, vomiting, and bloody stools. The classic triad was found in only 21% of cases and two symptoms were found in 70% of cases in one series of patients with intussusception (1). The colicky abdominal pain usually appears first and is the most common symptom. The pain is intermittent lasting for 4 to 5 minutes. It may return in 5 to 30 minute intervals. The patient may pull up his knees with crying. In between the episodes the patient may be asymptomatic. The patient may develop vomiting (90% of cases). The emesis may become bilious because of the obstruction. Bloody stools, found in 50% of cases, can be a late sign of intussusception. The absence of blood (even occult blood) does not rule-out intussusception. Patients with an intussusception may also present with lethargy/altered level of consciousness and pallor. The etiology of this lethargic presentation is not known, but it tends to occur in younger infants. Some hypothesize that this is due to release of endogenous opioids or endotoxins released from ischemic bowel. Intussusception in a child presenting with lethargy is often difficult to diagnose since other causes of lethargy such as dehydration, hypoglycemia, sepsis, toxic ingestion, post-ictal state, etc., must also be considered.

The physical examination of a patient with an intussusception may be unremarkable. If the patient is between attacks of the crampy abdominal pain, he may appear normal and the abdominal examination may be unrevealing. Also, examining the abdomen of an active or

crying child can often be difficult. Lethargic or tired infants with very soft abdomens are the easiest to examine. In some patients, a mass may be palpable in the right upper quadrant. It is often described as sausage-shaped. A sausage-like mass in the right upper quadrant and emptiness (the absence of bowel) in the right lower quadrant is clinically indicative of an intussusception. Blood may be found on rectal examination. If the intussusception has been present for a longer period of time, the abdomen may be distended and there may be findings of peritonitis.

There are several findings described on plain film abdominal radiographs of patients with intussusception. There may be evidence of a soft tissue mass or signs of bowel obstruction (air fluid levels and distended loops of bowel). The absence of gas in the right lower quadrant or flank may be seen with an intussusception. A target sign, crescent sign or indistinct liver margin sign may be present. A target sign is viewing the intussusception on cross-section which appears as two concentric circles (created by bowel fat density differences) usually in the right upper quadrant. The crescent sign is formed by the leading edge of the intussusception outlined by gas in the colon forming a crescent (intussusceptum protruding into a gas filled pocket). The absent liver margin sign can be seen if the soft tissue mass of the intussusception is resting at the hepatic flexure of the colon or there is absence of gas in the right upper quadrant making the lower edge of the liver indistinct. Free air may be visible on the radiograph if there has been intestinal perforation. An abdominal series may be normal especially early on. More recently, ultrasound has been advocated as it is highly specific (100%) and sensitive (98%) in making the diagnosis of intussusception, but only when interpreted by highly skilled radiologists. It may be helpful with confirming the diagnosis if an enema is contraindicated. The major problem with utilizing ultrasound is that it must be able to definitively rule out intussusception, since if diagnostic uncertainty still exists following the ultrasound, a contrast enema must still be performed. Additionally, if the ultrasound does identify an intussusception, a contrast enema must still be performed to reduce the intussusception. Thus, before considering an ultrasound, the diagnostic ultrasonography skills of the available radiologist must be determined. The high specificity and sensitivity percentages are published from studies done in ultrasound pediatric super centers and thus, these numbers are not necessarily applicable to general radiologists.

A barium enema has been the gold standard in the past for confirming the diagnosis and nonsurgical reduction of an intussusception. Water-soluble contrast has been used and more recently air enema reduction has been introduced. There are several reasons why radiologists have different preferences for which type of contrast they choose to use for the procedure. After the radiologist reduces the intussusception, they look for the contrast to reflux into the ileum. This is necessary to eliminate the possibility of an ileoileal intussusception. This is more difficult to see with an air contrast enema compared to a barium or water-soluble contrast enema. Air leaking into the peritoneal cavity because of intestinal perforation may also be difficult to see. Those in favor of using the air contrast enema technique argue that with perforation, the sudden loss of pressure would signal to the radiologist to stop the procedure. If a tension pneumoperitoneum results, this should be decompressed immediately with an 18-gauge needle. Barium leaking into the peritoneal cavity may cause a chemical peritonitis. Using a water-soluble contrast may decrease this complication. An air contrast enema is advocated as the preferred method by many pediatric radiologists (2), but since there is no clear consensus among radiologists of the best contrast enema option, this decision is best left to the radiologist performing the contrast enema procedure. The success rate of nonsurgical reduction is about 60% to 80%. Several factors are associated with a contrast enema being unsuccessful in reducing the intussusception. These include ileo-ileocolic intussusception, longer duration of symptoms (>12 hours), dehydration, small bowel obstruction, and age greater than 2 years or less than 3 months. The intussusception being present for 24 hours or more, is no longer a contraindication for attempting contrast enema reduction. The rate of intestinal perforation with nonsurgical reduction of an intussusception is 1% to 3%. A contrast enema is contraindicated in patients who have a bowel perforation, shock, or peritonitis. Ultrasound has also been used to monitor reduction of the intussusception using saline rather than contrast under fluoroscopy. The advantage of using ultrasound is that there is no radiation exposure. This is not commonly used in the United States. Computed tomography can also identify an intussusception. This usually occurs incidentally when the patient is having a CT scan for the evaluation of abdominal pain and intussusception was not initially suspected. If the intussusception is not reduced by an enema, or if there is intestinal perforation, shock, or peritonitis present, the patient is sent for surgical reduction. An intravenous line, a nasogastric tube, and consultation with a surgeon should be considered. If the patient is dehydrated, a fluid bolus with NS or LR should be given.

If the intussusception is reduced successfully by enema, some may discharge the patient home from the emergency department after observing the patient. However, most feel that the patient should be observed in the hospital for 24 hours. The risk of recurrence is about 4%. Intussusception recurs in up to 5% to 10% of the cases reduced by contrast enema and about 1 to 5% of those reduced by surgery, though most recurrences are late recurrences (after the patient has been discharged).

Questions

1. The most common type of intussusception is:
    a. ileoileal
    b. colocolic
    c. ileocolic
    d. ileo-ileocolic

2. Contraindications for non-surgical reduction of an intussusception include all of the following except:
    a. symptoms for longer than 24 hours
    b. shock
    c. intestinal perforation
    d. peritonitis

3. Which is the most common pathological lead point found with intussusception?
    a. neoplasm
    b. appendicitis
    c. polyps
    d. intestinal duplication
    e. Meckel's diverticulum

4. A pathologic lead point can be identified in approximately what percentage of patients with intussusception?
   a. 1%
   b. 5%
   c. 10%
   d. 15%
   e. 25%

5. The "classical triad" of symptoms of intussusception include:
   a. diarrhea
   b. vomiting
   c. fever
   d. bloody stools
   e. abdominal pain

6. Which element of the "classical triad" usually appears first?
   a. diarrhea
   b. vomiting
   c. fever
   d. bloody stools
   e. abdominal pain

7. All three of the "classical triad" of symptoms is found in what percentage of patients with intussusception?
   a. 9%
   b. 21%
   c. 50%
   d. 70%
   e. 90%

8. True/False: A normal abdominal series rules-out intussusception.

9. If a mass is palpable on physical examination, it is most often found in the:
   a. right upper quadrant
   b. right lower quadrant
   c. left upper quadrant
   d. left lower quadrant

Related x-rays

Intussusception Case and Radiographs: Young LL, Yamamoto LG. The Stomach Flu? - The Target, Crescent, and Absent Liver Edge Signs. In: Yamamoto LG, Inaba AS, DiMauro R. Radiology Cases In Pediatric Emergency Medicine, 1994, volume 1, case 2. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v1c02.html

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Answers to questions

1.c, 2.a, 3.e, 4.c, 5.b,d,e, 6.e, 7.b, 8.false, 9.a

Chapter X.5. Malrotation and Volvulus
Loren G. Yamamoto, MD, MPH, MBA

A 6 year old male is brought to the ED with a chief complaint of abdominal pain and vomiting. He has vomited 15 times since the onset of illness 30 hours ago. He is complaining of diffuse abdominal pain. His mother was attempting to give him small amounts of juice at a time, but this was not succeeding. He feels weak and he looks pale. His urine output is diminished. He was completely normal prior to the onset of vomiting. He has no fever, diarrhea, dysuria or coughing. His past history is significant for two previous episodes of severe abdominal pain associated with about 3 episodes of vomiting which resolved on its own. The first episode occurred at age 3 and the second episode occurred at age 5.

Exam VS T37, HR 100, RR 30, BP 110/70. He is moderately ill appearing; pale and somewhat weak. His eyes are sunken. His oral mucosa is moist. Neck supple. Heart regular. Lungs are clear. Abdomen is soft and mildly tender all over. Bowel sounds are diminished. He has no inguinal hernias and his testes are normal. His back is non-tender. His skin turgor is diminished.

An abdominal series is obtained which shows an obvious bowel obstruction. A surgeon is consulted and at laparotomy, his entire small bowel is found to be necrotic due to a midgut volvulus. The necrotic small bowel requires resection. He is admitted to the ICU post operatively. He develops shock requiring aggressive fluid resuscitation, pressors and inotropes. He eventually survives, but he will require parenteral nutrition for the rest of his life, since he does not have enough small bowel to survive with enteral nutrition.

Malrotation of the intestine refers to an intestinal malformation in which the intestines are suspended by a stalk rather than a broad fan of peritoneum. The term "malrotation" emphasizes the embryology of the malformation. From a clinician's standpoint, it is probably best to forget this since it is merely confusing trivia of little clinical importance.

In malrotation, the intestines function normally, so the patient is entirely asymptomatic until a complication of the malrotation occurs. Malrotation should really be renamed to "guts on a stalk syndrome" because this is the clinical feature that causes the major complication of malrotation in which the peritoneal attachments suspend the intestines like a stalk rather than a broad fan. If the attachment of the intestine to the peritoneum and abdominal wall is normal, it is broad extending from the right lower quadrant, across the back of the abdominal wall toward the left upper portion of the abdomen. This broad attachment (like a rectangular flag) makes it difficult or impossible for the intestinal loops to twist and cause an obstruction. However, in malrotation, the intestines are suspended from a narrow attachment to the back of the abdominal wall, which makes the intestines highly susceptible to twisting about this stalk (guts hanging on a stalk). This is called a midgut volvulus. Once the stalk twists, there is a fair likelihood that it will untwist on its own, relieving the volvulus. However, if this fails to occur, or if it twists the wrong way to make the twist tighter, blood flow to the intestines is interrupted, and this midgut volvulus eventually results in a catastrophic bowel infarction. This is why, this syndrome should be renamed "guts on a stalk syndrome".

Note that the patient in our case example had two previous episodes of vomiting with abdominal pain which resolved on its own. These could have been episodes of "intermittent volvulus" which occurs when the volvulus just happens to twist, then untwist on its own. If the clinician is really smart, it may be possible to diagnose a malrotation just from a history or clinical pattern consistent with an intermittent volvulus. How can a malrotation be diagnosed if the patient does not have a midgut volvulus at the time? An upper GI series will show that the junction of the duodenum and jejunum are misplaced. A barium enema may identify that the cecum is not in the right lower quadrant where it should be, which is indicative of a malrotation; however, this finding is not as reliable as the upper GI series findings. An ultrasound may be able to identify a misplacement of the superior and inferior mesenteric axes coming off the descending aorta which is indicative of a malrotation, but again, this sign is not 100% diagnostic.

Malrotation may also present with a less severe form of a bowel obstruction in which the stalk of the peritoneum known as Ladd's bands, may overlie and compress the underlying bowel causing a bowel obstruction. This does not necessarily occur with a midgut volvulus which is much more serious.

Otherwise, the presentation of a malrotation is with an acute bowel obstruction caused by a midgut volvulus. This diagnosis must be made IMMEDIATELY because only prompt surgical intervention can relieve the volvulus which restores perfusion to the bowel, to prevent a catastrophic bowel infarction. The anatomy of a midgut volvulus is such that the bowel infarction that results is truly catastrophic since it often involves the entire small bowel. This results in substantial tissue necrosis and complications such as shock and sepsis. If the patient is able to survive this, parenteral nutrition is required for the remainder of his/her life since there is not enough bowel remaining for enteral nutrition.

Midgut volvulus should not be confused with sigmoid volvulus which generally occurs in adults. Sigmoid volvulus involves the large bowel and can often be decompressed by barium enema or other non-surgical procedures. In a sigmoid volvulus, the sigmoid is excessively lengthy. It has a tendency to twist upon itself resulting in a sigmoid obstruction. Abdominal radiographs demonstrate a gas distended sigmoid colon. Non-surgical reduction measures are usually successful.

This is opposed to a midgut volvulus, which occurs mostly in children with a malrotation. Approximately half the cases of malrotation will present during the neonatal period with an acute bowel obstruction. However, the other cases can present with an acute bowel obstruction at any time.

Questions

1. What are the two mechanisms of a bowel obstruction associated with malrotation?
2. Does the term "malrotation" refer to any patient condition, symptom or malformation description that is relevant for clinicians?
3. What is the most reliable imaging procedure to identify or rule out a malrotation in the absence of a midgut volvulus?
4. Name two different types of intestinal volvulus and describe how they are different.
5. Is it likely that one could have a malrotation and never have a volvulus throughout life?

Related x-rays

Malrotation and volvulus: Rosen LM, Yamamoto LG. Abdominal Pain and Vomiting in a 7-Year Old. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1995, volume 2, case 8. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v2c08.html

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Answers to questions

1. a) Ladd's bands compressing and obstructing the proximal small bowel. b) Midgut volvulus.

2. The term "malformation" originates from the embryological formation of the malrotation which is of little or no value for clinicians.

3. Upper GI series. Barium enema and ultrasound are less reliable.

4. Midgut volvulus and sigmoid volvulus. Midgut volvulus is a true surgical emergency involving nearly the entire small bowel which will infarct unless the volvulus is relieved surgically. Sigmoid volvulus, which occurs in the elderly, involves the sigmoid colon and can usually be relieved without surgical means.

5. It is unlikely, but it can happen. About half the patients with a malrotation will present in the neonatal period, with the other half presenting at any other age.

Chapter X.6. Gastroschisis and Omphalocele

Rodney B. Boychuk, MD

A newborn male infant is born to a 21 year old G2P1 mother at 36 weeks gestation via cesarean section. Appropriate antenatal care and monitoring occurred throughout the pregnancy. Prenatal ultrasonography was done at 32 weeks gestation revealing what appeared to be free intestine floating in the amniotic fluid, coming from the anterior abdominal wall. The mother elected for a cesarean section delivery after fetal lung maturation was assured (at 36 week gestation in this case scenario). The baby looks normal at birth except for matted intestinal loops coming through an anterior abdominal wall defect just to the right of the umbilical cord. The loops are very edematous and do not resemble normal intestines. Treatment in the delivery room includes evaluation of the ABCs, then the intestines are wrapped with saline soaked sterile gauze (well padded with no pressure), followed by dry sterile dressings to minimize heat loss. Placement of a nasogastric tube to decompress the stomach and warming for maintenance of a normal temperature are done next. No attempt is made to force the exteriorized intestines back into the abdominal cavity. The patient is transported to NICU where the neonatologists first take care of his medical needs, and a pediatric surgeon is consulted.

Omphalocele (OC) and gastroschisis (GS) are congenital defects of the anterior abdominal wall. They are usually associated with gut abnormalities, including abnormal rotation and fixation. Although the midgut is usually nonrotated, complications secondary to this including volvulus are infrequent, and duodenal obstruction from Ladd's bands is rare. Both these conditions (OC and GS) are obvious at birth.

An omphalocele arises at the umbilical ring as a central defect secondary to developmental arrest of layers of the abdominal wall. Embryologically different, a gastroschisis involves the base of the umbilical stalk, with the defect in the abdominal wall always occurring lateral to the base of the umbilicus, through which a portion of the intestine has escaped (usually the right side). Originally confused as a type of omphalocele, gastroschisis is now recognized as a separate entity. This defect may represent an isolated congenital defect in the abdominal wall, or be the result of closure of the celomic cavity while a portion of the intestinal tract remained trapped outside the abdomen, at the base of the umbilical cord. The intestines float freely in the amniotic fluid.

The diagnosis of both types of anterior abdominal wall defects are frequently made antenatally by ultrasound, as early as 12 weeks gestation. Diagnosis is made entirely by inspection and is readily apparent after delivery. Striking differences between the two are obvious. An omphalocele is usually covered by a translucent membrane overlying the bowel and solid viscera. Size varies from a small hernia of the cord (1 to 2 cm in diameter), to a huge mass containing essentially all the abdominal viscera. Usually, the sac remains intact, but it occasionally ruptures during delivery. The defect is always within the umbilical ring. The sac may contain bowel, stomach, and

liver. Omphaloceles are often associated with other congenital malformations and with abnormal karyotypes. Occasionally, the bowel is attached to the sac.

Alternatively, the defect of gastroschisis is lateral to the umbilicus. This has allowed the escape of the intestine into the amniotic cavity at different times in fetal development. Therefore, the appearance of the intestines are variable. Some appear edematous and matted that have been exposed to the amniotic fluid for many weeks, while other intestines are glistening and normal looking, as they "escaped" just before birth. There is no sac, and the liver does not protrude.

The immediate treatment in the delivery room is similar for both conditions. The abdomen (omphalocele) or exteriorized intestine (gastroschisis) is wrapped with saline soaked sterile gauze (well padded with no pressure), followed by dry sterile dressings to minimize heat loss. Placement of a nasogastric tube to decompress the stomach and maintenance of a normal temperature are essential. No pressure is placed on the omphalocele and there should be no attempt to reduce it. This maneuver may rupture the sac, interfere with venous return, and/or impede the infant's respiratory effort. Similarly, no attempt should be made to force the exteriorized gastroschisis intestine back into the abdominal cavity.

Although the definite treatment is surgical, delay in closure has no adverse outcome. Therefore, it is essential that optimal resuscitation occur prior to surgery. The general consensus on operative management of abdominal wall defect is to provide primary closure, if it can be achieved without hemodynamic or respiratory compromise. Patients with primary closure have better survival rates, reduced risk of sepsis and overall, a shorter hospital stay.

Although smaller omphaloceles usually undergo primary closure, giant omphalocele in the neonate is a challenging surgical emergency that requires individualized approaches to operative repair. In general, omphaloceles greater than 6 cm in diameter require silo reduction with silastic interwoven with Marlex. A silo is first created, by placing the intestines into what looks like a plastic bag turned upside down, with the edges of the bag sewn to the edges of the opening in the abdomen. This essentially creates an "artificial abdomen". The contents of the bag are squeezed daily from the top down, slowly forcing the intestines back into the abdomen. Over days to weeks the intestines are pushed back into the abdomen, and the abdominal wall is finally closed.

Interesting methods have recently been described utilizing continuous controlled pressure to achieve smooth, rapid, and safe silo reduction of an anterior abdominal wall defect. One example includes a metal tube with larger wheels at each end that is suspended by runners and counterweights, to slowly roll the silo and squeeze the contents into the abdominal cavity.

More recently a silastic spring-loaded silo (SLS) has been used routinely (in one center) for infants with gastroschisis. These surgeons found that SLS, followed by elective repair, permitted gentle, gradual reduction in the viscera. SLS was associated with lower airway pressures, earlier extubation, fewer complications, and decreased length of stay and hospital charges.

Regardless of the methods, the principles of the silo technique rely on steady pressure on the prosthesis, and a reduction in size over several days, to bring about gradual reduction of the intestines. Finally, once reduced, surgical closure can be accomplished. Irrigation with povidone-iodine (Betadine) solution or coverage with a layer of silver sulfadiazine cream (Silvadene) is effective in reducing surface contamination throughout the time for which the prosthesis is required.

Although the survival rate of patients with abdominal wall defects has gradually improved with the advances in the diagnostic and treatment modalities, the outcome is largely dependent on coexisting anomalies. Omphaloceles are often associated with abnormal karyotypes (trisomy 13, 18, and 21) or congenital malformations. In a recent review, 10 of 31 cases of omphalocele (OC) and 4 of 11 cases of gastroschisis (GS) cases, multiple congenital anomalies were diagnosed. The birth weight was below the 10th percentile in 23% of OC and 36% of GS cases. An abnormal prenatal karyotype was established in 5 of 25 OC cases versus none in the GS group. In 36 cases, an expectant obstetric management was followed, and in six OC cases, the pregnancies were terminated because of severe multiple anomalies (3 cases) or an abnormal prenatal karyotype (3 cases). The preterm delivery rate (excluding terminations) was 12 of 25 in the OC group versus 8 of 11 in the GS group. The cesarean section rate was almost identical (19% versus 18%) in both subgroups, the majority of which were performed to protect the abdominal wall defect. The overall survival rate was 39 per cent in the OC group compared to 72% in the GS group.

The surgeon must be aware of other associated defects. Congenital malrotation of the colon usually occurs in patients born with an omphalocele. Although not a serious defect, the anomaly can lead to midgut volvulus and intestinal obstruction in a baby who has previously recovered from treatment of an omphalocele, and therefore must be corrected at the time of initial surgery.

A different defect, intestinal atresia, occurs in about 10% of patients with GS. In these infants, the clinical course is one of early complete obstruction, which requires abdominal exploration if the lesion has been inadvertently overlooked at the time of initial repair of the gastroschisis. Rarely, there is a short gut from an antenatal volvulus.

Even after successful reduction of the bowel and closure of the defect, normal motor function of the gut may be delayed for weeks to months in cases of gastroschisis. Although long term outcome of these patients is generally good, they have high incidence of gastroesophageal reflux (GER) (40-50%) for which they should be closely monitored. Parenteral nutrition and intensive care have markedly improved survival.

A recent follow-up study was done involving patients post-operatively, from 1-28 years prior. Primary closure was possible in 25 omphalocele (OC) and 20 gastroschisis (GS). Eighteen children with OC and 8 with GS suffered from additional abnormalities, which were treated simultaneously. Twenty percent of the babies with OC died mostly because of severe congenital anomalies and 12.9% of GS because of infectious complications in combination with other diseases. There were fewer neonatal deaths in the last decade, attributed to better operative and perioperative treatment, as well as abortions following improved ultrasound diagnosis (as early as 12 weeks gestation).

Long-term follow-up revealed normal growth and development, except for those with severe congenital anomalies. Late surgical problems have also recently been studied. A questionnaire concerning late surgical problems was distributed to the parents of 47 surviving children. The mean follow up time was 5.4 years. There was no mention of remaining problems regarding 16 of the 28 omphalocele patients and 10 of the 16 gastroschisis patients. Postoperative abdominal wall hernia was reported in 7 OC cases and in 6 GS cases. Postoperative intestinal obstruction occurred in 4 OC cases and 1 GS case. The other complications were related to abdominal pain, cryptorchidism, constipation and difficulties with care of the intestinal stoma. All the remaining problems could be corrected and the long-term results in both conditions were good.

In summary, an omphalocele or gastroschisis are congenital defects of the anterior abdominal wall. An omphalocele arises within the umbilical ring as a central defect, while a gastroschisis involves the base of the umbilical stalk, with the defect in the abdominal wall always occurring lateral to the umbilicus. Although the diagnosis of both types are frequently made antenatally by ultrasound, if missed, they are readily apparent after delivery in the delivery room, where striking differences between the two are obvious. Although the survival rate of patients with abdominal wall defects has gradually improved, the outcome is largely dependent on coexisting anomalies.

Although surviving children without severe congenital anomalies have a good quality of life, late surgical problems are seen, and close follow-up is essential to good outcome.

Questions

1. The earliest way to diagnose an anterior abdominal wall defect is:
    a. by physical exam
    b. by history
    c. by fetal ultrasound
    d. by fetal CT scan

2. The following are correct regarding omphaloceles except:
    a. is usually covered by a translucent membrane
    b. is frequently associated with other congenital malformations
    c. is lateral to the umbilical stump
    d. is within the umbilical ring

3. The following are true about gastroschisis:
    a. occurs lateral to the umbilical stump
    b. can be diagnosed antenatally
    c. at birth often have edematous matted intestinal loops
    d. all of the above

4. Treatment of abdominal wall defects includes:
    a. immediate surgical repair
    b. pushing the intestines back into the abdominal cavity while still in the delivery room
    c. provide immediate optimal resuscitation and stabilization first, and then surgery
    d. always do primary closure in both lesions

5. The true statement below is:
    a. The surgeon does not need to worry about other associated defects as the neonatologist will already have treated them.
    b. There are essentially no late surgical problems after repair.
    c. Improved ultrasound diagnosis has resulted in some women seeking termination of pregnancy as early as 12 weeks gestation.
    d. The long term outcome of survivors reveal poor growth and development.

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Answers to questions

1. c
2. c
3. d
4. c
5. c

Chapter X.7. Diaphragmatic Hernia
Rodney B. Boychuk, MD

A newborn male infant is born to a 23 year old G2P1 mother at 39 weeks gestation via NSVD (normal spontaneous vaginal delivery). Appropriate antenatal care and monitoring occurred throughout the pregnancy. As there were no significant antenatal problems, no prenatal ultrasonography was done. Immediately following delivery, the baby looks "normal". He cries immediately, however, at 1 minute of age, he remains very cyanotic. The neonatal resuscitation team is called to the delivery room. At 5 minutes of age, the baby remains very cyanotic, tachypneic and dyspneic, despite 100% oxygen via mask. The resuscitation team starts bag-mask positive pressure ventilation with 100% oxygen, but the baby becomes bradycardic, therefore he is intubated and ventilated. Auscultation of the lungs reveal good breath sounds in the right chest, but no breath sounds in the left. The heart sounds seemed loudest in the right chest, and the abdomen appears scaphoid. Ventilation is continued through the endotracheal tube, while an NG tube is inserted and suction is applied. A STAT chest x-ray is done, which reveals bowel (and the NG tube tip) in the left chest cavity. The baby is transferred to the NICU. This is a case of congenital diaphragmatic hernia presenting in the delivery room.

Although congenital diaphragmatic hernia (CDH) is rare (approximately 1 in 3000 births) it is associated with high mortality, morbidity, cost and suffering. Embryologically, by the end of the 12th week of gestation, fetal bowel has returned to the abdominal cavity and the formation of the diaphragm is complete, separating the intrathoracic from the intra-abdominal contents. Failure of this to occur results in a persistent pleuroperitoneal canal (foramen of Bochdalek), which allows the intra-abdominal viscera to occupy the chest cavity. This in turn prevents the lungs from developing, resulting in lung hypoplasia, worse on the side of the hernia. Although in the case above the diagnosis was not made until after delivery, with increasing use of fetal sonography, the diagnosis is commonly made prenatally, often as early as 15 weeks gestation. Unfortunately, more than 40% have associated anomalies of their brain, heart or other regions resulting in a poorer prognosis.

Classically, if undiagnosed prenatally, these infants present as a "neonatal emergency" in the delivery room. They do not respond to the typical steps of neonatal resuscitation, and usually get worse with bag-mask ventilation (BMV). With left sided CDH, breath sounds are diminished or absent in the left chest and because the mediastinum is displaced to the opposite side, the heart sounds are heard louder in the right chest. As the stomach and bowel fill with gas, (made worse by BMV), respiration and cardiac action are further compromised, and hypoxia and respiratory acidosis worsens. The neonate exhibits progressive respiratory distress, cyanosis and ultimately bradycardia. Because the abdominal contents are displaced into the chest, the abdomen often is scaphoid. Cases have been reported in which the infants remain relatively asymptomatic in the early hours and days of life. Rarely, a diaphragmatic hernia presents in an older child, as an incidental finding on physical exam or chest x-ray, or may be "acquired" as a result of traumatic rupture of the diaphragm secondary to a severe blow to the abdomen.

From the practical standpoint, 90% of congenital diaphragmatic hernias (CDH) occur on the left side. If the diagnosis is suspected clinically (but not yet confirmed), never bag-ventilate the infant. Rather, intubate, and apply "gentle" positive pressure ventilation. Secondly, pass a nasogastric catheter and apply intermittent suction to decompress the stomach (occupying the thorax and acting similar to a tension pneumothorax). These two measures alone may result in considerable clinical improvement. An emergency chest x-ray is mandatory to confirm the diagnosis. On x-ray, the air-filled bowel is seen occupying the left hemithorax, with resultant displacement of the mediastinum to the right. However, CDH has been misdiagnosed as a left tension pneumothorax, with acute respiratory distress temporarily relieved by needle aspiration. This x-ray finding of a "hyperlucent hemithorax" due to intrathoracic gastric dilatation alone is a unusual presentation of CDH in neonatal period, but can lead to a delayed diagnosis. Always look at the abdomen on x-ray, as absence of the stomach bubble in the left upper quadrant of the abdomen is an important radiologic clue to make the diagnosis.

The differential diagnosis must also include any neonatal emergency that presents with respiratory failure within minutes of birth. The clinical and radiological presentations are variable, making the diagnosis of a right-sided diaphragmatic hernia even more difficult. Careful evaluation of the clinical presentation, ultrasonography and chest films are mandatory for precise diagnosis. The liver partially blocks the pleuroperitoneal canal and limits the amount of bowel that can herniate into the chest. Symptoms in infants with right-sided hernias may be less severe, but the management is the same.

As with any form of ventilation, positive pressure can result in a pneumothorax on the contralateral side, which must be carefully observed for. If unrecognized, this can be a disastrous complication, resulting in death.

The infant born with congenital diaphragmatic hernia (CDH) remains one of the most complex patients to manage. Pulmonary hypoplasia and immaturity of the lungs remain the leading cause of death, from pulmonary hypertension (right-to-left shunting) with resultant hypoxemia. Over the last decade, there has been a constant improvement in the understanding of the pathophysiology of CDH and its management. Based on the knowledge that CDH is more of a physiological disease than a surgical disease, management strategy has shifted from immediate repair to delayed repair preceded by stabilization. However, the ideal treatment remains elusive. The old management strategy of immediate surgery is now replaced by the principle of physiologic stabilization and delayed surgery. Conventional ventilatory techniques, with high pressures and hyperventilation used to reverse ductal shunting and cause alkalinization, are now being replaced with ventilatory techniques utilizing the concepts of permissive hypercapnia and high frequency oscillation ventilation. The complications of ventilation including air leaks, barotrauma and consequent bronchopulmonary dysplasia are at least in part circumvented because of these newer techniques. Regardless of the treatment, the goal is to reverse the persistent pulmonary hypertension causing right to left shunting through the ductus arteriosus and foramen ovale.

Another recent development is the use of inhaled nitric oxide. Endogenous nitric oxide is an important modulator of vascular tone in the pulmonary circulation. Initial studies indicated that inhalation of nitric oxide results in a reduction in pulmonary hypertension, with improvement in oxygenation but no change in the systemic vascular resistance. However, no such beneficial effect has as yet been consistently reported in infants with congenital diaphragmatic hernia. Inhaled nitric oxide has side effects, although those due to nitrogen dioxide and methemoglobin formation can be minimized by using the smallest effective nitric oxide dose, continuous nitric oxide and nitrogen dioxide monitoring and frequent methemoglobin analyses. Longer term follow-up studies are needed to determine the true risk:benefit ratio of inhaled nitric oxide treatment in newborns with CDH.

Extracorporeal membrane oxygenation (ECMO) has been shown to salvage some of the most severely affected neonates. As some infants do not improve despite aggressive therapy, some centers use ECMO before hernia repair to stabilize these critically ill infants. Venovenous or venoarterial bypass is used, depending on the infant's hemodynamic stability. Bypass is continued until the pulmonary hypertension is reversed and lung function is improved, usually between 7 and 10 days of age. Approximately 60% of infants with CDH

who are supported by ECMO survive. Despite this aggressive therapy, there are newborns with such severe pulmonary hypoplasia that all forms of life support are futile.

Other advanced and experimental respiratory therapies merit investigation. Further insights into the pathophysiology of CDH and the introduction of less invasive therapeutic techniques such as high frequency oscillation ventilation, inhalation nitric oxide, surfactant, and perfluorocarbon liquid ventilation may make the need for ECMO redundant.

Once medically stable, the definite treatment is surgical. The surgeon reduces the hernia gently by withdrawing the viscera from the chest. There may be enough diaphragmatic tissue to complete a direct suture repair. However, if a large portion of the diaphragm is missing, prosthetic material must be used to repair the defect. A chest tube is usually placed in the left hemithorax and brought out through an intercostal space. As the abdominal contents have been in the thorax for most of fetal development, the abdomen often does not have enough room for the "missing" contents. Forcing the contents into the abdomen will compress the vena cava and compromise respirations by pushing up on the diaphragm. The surgeon may be forced to omit total anatomic closure of the abdominal wall, and utilize skin flaps with only the skin being closed. An alternative is to create a silastic silo like those used for gastroschisis or a large omphalocele (see Gastroschisis and Omphalocele chapter). The pouch created accommodates the intra-abdominal organs, and diaphragmatic action and venous return are unimpeded. The final repair is completed after the infant has been weaned off the ventilator and is clinically stable.

Fetal surgery for congenital diaphragmatic hernia and other fetal conditions has been considered. However, at this time, open fetal surgery has proven too invasive to be justified for the treatment of diaphragmatic hernia, and progress in postnatal therapy (including ECMO) has dramatically improved the neonatal outcome in all but the most severely affected infants.

The outcome of congenital diaphragmatic hernia differs depending on the stage of the fetus or infant's life (i.e., antenatal, immediate postnatal, and postoperative). A review of the available literature on the outcome of CDH from 1985 to March 1998 (35 studies) revealed the median overall mortality was 58% for babies diagnosed in utero, 48% if born alive, and 33% postoperatively (lower mortality in this group that was stable enough to reach surgery). Although one may expect a poorer outcome with earlier intrauterine diagnosis, ultrasound, diagnosis before 25 weeks of gestation was not found to be a uniformly bad prognostic indicator (median mortality, 60%). However, outcome was worse for those fetuses with other congenital anomalies (median mortality, 93%). ECMO appears to improve survival. The median percentage mortality for all infants born alive and treated in ECMO centers was 34%, while the median percentage mortality for all ECMO-treated infants was 44%.

Unfortunately, surviving the initial repair doesn't assure future well being. Survivors of CDH usually have persistent pulmonary and nonpulmonary problems to deal with. Many of these patients require bronchodilators, oxygen, diuretics, and corticosteroids for obstructive airway disease and bronchopulmonary dysplasia. They are at high risk from respiratory syncytial virus (RSV) and should receive RSV immunoprophylaxis. Pulmonary problems continue to be the major source of morbidity for survivors of CDH long after discharge. Although the need for ECMO and the presence of a patch repair are both predictive of more significant morbidity, non-ECMO CDH survivors also require frequent attention to pulmonary issues beyond the neonatal period. There is a need for long-term follow-up of CDH patients preferably with a multidisciplinary team approach. Hopefully, future developments in medical therapy will continue to decrease the mortality and morbidity of patients with CDH.

In summary, if not diagnosed antenatally by sonography, CDH presents as a neonatal emergency in the delivery room, with a normal appearing infant not responding to resuscitation. Endotracheal intubation with gentle ventilation, followed by nasogastric suctioning is immediately indicated. Pulmonary hypoplasia and pulmonary hypertension with right-to-left shunting are common with resultant hypoxemia. The old management strategy of immediate surgery is now replaced by the principle of physiologic stabilization and delayed surgery. Other advanced and experimental respiratory therapies merit investigation. Further insights into the pathophysiology of CDH and the introduction of less invasive therapeutic techniques such as high frequency oscillation ventilation, inhalation nitric oxide, surfactant, and perfluorocarbon liquid ventilation may replace the need for ECMO. However, the ideal treatment remains elusive

Questions

1. The earliest way to diagnose a diaphragmatic hernia is:
    a. by physical exam
    b. by history
    c. by fetal ultrasound
    d. by fetal CT scan

2. The following are correct regarding diaphragmatic hernia except:
    a. is usually on the left side
    b. is frequently associated with hypoplastic lungs
    c. can present similar to a tension pneumothorax
    d. is frequently asymptomatic at birth

3. The following are true about diaphragmatic hernias:
    a. often have scaphoid abdomen on exam
    b. can be diagnosed antenatally by ultrasound
    c. at birth often have persistent cyanosis and respiratory distress
    d. all of the above

4. Treatment of diaphragmatic hernia includes:
    a. immediate surgical repair
    b. pulling the intestines back into the abdominal cavity while still in the delivery room
    c. provide immediate optimal resuscitation and stabilization first, and then surgery
    d. always do primary closure of the diaphragm

5. The true statement below is:
   a. The surgeon does not need to worry about medical problems as the neonatologist will already have treated them.
   b. There are essentially no medical problems after surgical repair.
   c. Improved ultrasound diagnosis has resulted in some women seeking termination of pregnancy.
   d. The long term outcome of survivors reveals no significant chronic pulmonary problems.

Related x-rays

Late onset diaphragmatic hernia: Yamamoto LG. Diminished Breath Sounds and Air in the Chest. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1994, volume 1, case 6. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v1c06.html

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Answers to questions

1. c
2. d
3. d
4. c
5. c

Chapter X.8. Pyloric Stenosis
Kevin H. Higashigawa, MD

This is a 3 week old male infant who presents to the emergency department with a chief complaint of vomiting x 3-4 days. His mother states that the vomiting has gotten progressively worse and now seems to "shoot out of his mouth." The emesis always occurs after feeding, sometimes vomiting the entire volume of his feed. The vomitus is non-bilious and non-bloody. After vomiting, the infant remains hungry and is still eager to feed. He is exclusively bottle fed with formula. There is no history of fever, URI symptoms, or diarrhea. He is less active than normal. He is making fewer wet diapers and less stool than usual. There is no history of trauma or recent travel. There are no ill contacts.

Exam: VS T 37.0, P 170, R 50, BP 80/50, O2 saturation 99% on RA. Length is 54 cm (50th percentile) and weight is 3.6 kg (25th percentile; previously 50th) and head circumference is 37 cm (50th). He is a well-developed, well-nourished male in no distress. His skin is normal. HEENT exam is normal. His neck is supple. Heart auscultation reveals tachycardia and a regular rhythm. Lungs are clear. His abdomen is slightly distended with active bowel sounds. No hepatosplenomegaly is noted. Attempting to palpate an olive mass is inconclusive. He has no inguinal hernias. Genitalia are normal. Extremities are normal. Color, perfusion, and capillary refill are good. Neurologic examination is normal.

CBC is unremarkable. Electrolytes: Na 131, K 3.2, Cl 95, bicarb 30. An IV fluid infusion is started. An abdominal series shows no obstruction, but the stomach is dilated. An ultrasound study confirms the diagnosis of pyloric stenosis. The patient undergoes a pyloromyotomy and recovers without complications.

Hypertrophic pyloric stenosis (HPS) is a common cause of GI obstruction in the young infant. HPS occurs in approximately 3 of every 1000 live births in the United States (1). Males are four times more likely to develop HPS than females. A familial pattern exists, although HPS does not follow classic Mendelian genetics. The risk for developing HPS is about 7% if the father was previously affected and about 10-20% if the mother was affected (1,2).

The manifestations of GI obstruction do not typically occur until about the 2nd to the 6th week of life (1). HPS presents after several weeks of life because the pylorus is normal at birth and hypertrophies as time progresses (2). The hallmark of gastric outlet obstruction is non-bilious vomiting. The vomiting occurs immediately after feeding and varies in intensity, depending upon the degree of stenosis present. Eventually, the vomiting increases in severity to become projectile and will typically involve the entire volume of the feed. Asking parents if the emesis is "projectile" is not very useful since, in the eyes of parents, ALL vomit "projects". Thus, a more discriminating question to ask, is to stand an arm's length from a wall and ask them if the emesis will hit the wall from that distance. If the answer is "yes", then it is projectile vomiting. After regurgitation, the infant will remain hungry and want to feed again. Approximately 8% of patients will have some degree of hematemesis related to gastritis or esophagitis (3).

The exact etiology of HPS is unclear. One theory proposes the lack of pyloric inhibitory innervation leading to reduced levels of nitric oxide, a smooth muscle relaxant. As a result, the pylorus experiences unopposed contraction following muscarinic stimulation (4). Elevated levels of prostaglandins have also been implicated owing to the increased incidence of pyloric stenosis in infants who have received PGE to maintain a patent ductus arteriosus. HPS has also been associated with other GI anomalies, such as tracheoesophageal fistula, pyloric atresia, antral webs, gastric duplications, and gastric volvulus. Furthermore, HPS has been linked to other disease states, such as eosinophilic gastroenteritis, epidermolysis bullosa, trisomy 18, and Turner Syndrome (1).

On physical exam, the infant may exhibit poor weight gain or even weight loss. Marasmus, however, or severe protein-calorie malnutrition, is rarely seen today. Jaundice may be seen in approximately 5% of infants (1). After feeding, a wave of gastric peristalsis may be seen traversing the abdomen from left to right, representing intense contractions against an obstruction. Abdominal distention may be a late finding, as is usually the case with proximal GI obstructions. The hypertrophied pylorus may be palpable. The pylorus is firm, mobile, and olive-shaped. It is located in the right upper quadrant of the abdomen, beneath the liver edge (1). It is best palpated from the left side while the infant is feeding since the abdominal muscles are relaxed. A palpable "olive" is pathognomonic of HPS (2), but it is very hard to feel in practice (requires experience to appreciate this accurately).

The diagnostic test of choice is the ultrasound, which has approximately 90% sensitivity (1). Criteria for diagnosis include an elongated pyloric channel (longer than 16 mm), an enlarged pyloric diameter (greater than 14 mm), and a thickened muscle wall (greater than 3.5 mm) (3). If an ultrasound is non-diagnostic but clinical suspicion remains high, an upper GI series may be helpful. Characteristic signs of HPS include an elongated pyloric channel with a "shoulder sign" (representing the hypertrophied pylorus bulging into the antrum) and streaks of barium flowing through the stenosed channel, producing either a single "string sign" or a "double track sign" (if there are parallel streaks) (1).

The "classic" laboratory finding in HPS is a hypochloremic, hypokalemic metabolic alkalosis. Repeated vomiting results in a loss of HCl, causing the hypochloremic metabolic alkalosis. The patient is likely dehydrated from repeated GI loss and poor oral intake. A metabolic acidosis (lactic acidosis) may result with severe dehydration. Due to more expedient diagnosis and treatment, however, more than 90% of patients with HPS do not typically present with any metabolic disturbance (5). Levels of glucuronyltransferase can be decreased in a small percentage of infants, as the liver is deprived of substrate from poor caloric intake, leading to an indirect hyperbilirubinemia (2).

The differential diagnosis of HPS is extensive. Vomiting in infants under 1 month of age is more likely due to a serious cause (often one requiring surgical intervention). Vomiting in older infants is more often secondary to gastroenteritis, but serious etiologies occur which may be difficult to diagnose.

Management of HPS initially consists of fluid replacement and management of electrolyte abnormalities to stabilize the patient. In the 1960s, HPS was treated medically with oral atropine, and surgery was reserved for sicker infants (4). However, due to the improvements in surgical technique and associated lower mortality and morbidity rates, as well as the rapidity of the resolution of symptoms, pyloromyotomy is now the treatment of choice. Currently, the mortality rate for pyloromyotomy is between 0 and 0.5% and can now be performed laparoscopically (1). HPS is not a surgical emergency. The infant should be fluid resuscitated prior to surgery and the patient's alkalosis should be resolved (bicarbonate level < 30 mEq/dL) to minimize anesthetic risk (3). Post-operative vomiting may occur secondary to edema of the pylorus at the incision site. In cases of incomplete pyloromyotomy, endoscopic balloon dilation has been successful. Of interest is that other countries may not treat HPS routinely with surgery, but rather IV fluid maintenance until the condition resolves with time in most instances. Pyloromyotomy is reserved for those infants who fail to improve.

Questions

1. What is the "classic" presentation of HPS?

2. How is HPS diagnosed?

3. What is the "classic" laboratory finding in HPS?

4. What is the initial step in management?

5. Which of the following sets of electrolytes could be seen with HPS (Na, K, Cl, bicarb):
   a. 130, 2.7, 90, 28
   b. 130, 5.8, 94, 22
   c. 130, 3.9, 98, 17
   d. 148, 4.1, 108, 13

Related x-rays

Yamamoto LG. Gastric Dilatation in a 2-Week Old. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1996, volume 5, case 17. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v5c17.html

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Answers to questions

1. A 3 to 4 week old male infant who presents with progressively severe, non-bilious vomiting, which may be projectile. The vomiting occurs immediately after feeding, after which the infant is still hungry and wants to feed again. On physical exam, the infant may display signs of dehydration. Visible waves of peristalsis may be seen and an "olive" may be palpable.

2. A palpable "olive" is pathognomonic but is very difficult to determine with certainty. If the pylorus cannot be palpated, ultrasound is diagnostic with 90% sensitivity.

3. The "classic" laboratory finding is a hypochloremic, hypokalemic metabolic alkalosis. However, due to more expedient diagnosis, this metabolic abnormality is seen in less than 10% of patients.

4. The initial step in management involves fluid resuscitation and correction of any metabolic abnormalities. HPS is not a surgical emergency, and any fluid deficits or alkalosis should be corrected prior to surgery to decrease surgical/anesthetic risks.

5. Electrolyte patterns are not pathognomonic for pyloric stenosis. The correct answers are a and c. Pattern "a" is a classic early vomiting picture, often seen with HPS. Pattern "c" is a picture of vomiting resulting in dehydration and lactic acidosis. This can also be seen later in the clinical course of HPS as dehydration worsens. Pattern "b" is typical of adrenal crisis (low Na, high K). Pattern "d" is typical of hypernatremic dehydration.

Chapter X.9. Intestinal Atresias, Duplications and Microcolon
Timur M. Roytman

This is a newborn infant male born to a 25 year old G1P1A0 mother at 36 weeks gestation via vaginal delivery. Mother received appropriate antenatal care throughout her pregnancy. The pregnancy was remarkable for polyhydramnios. The baby looked normal at birth, however, at 1 day of age (day 2 of life), the infant begins to vomit bilious material and appears jaundiced. Physical exam of the infant is remarkable only for jaundice. A pertinent negative finding is the absence of a distended abdomen.

A plain abdominal radiograph reveals a "double-bubble sign." His symptoms along with the radiographic findings are suggestive of duodenal atresia. Initial treatment consists of insertion of a nasogastric tube along with IV fluid replacement. An echocardiogram and radiographic studies of the spine are performed to evaluate for other congenital abnormalities. No other abnormalities are found and the patient is referred to surgery for surgical evaluation and treatment.

Atresia, by definition, is the absence of an opening of a hollow visceral organ, resulting in a complete obstruction (1). There are several types of atresias: esophageal atresia with and without tracheoesophageal fistula, duodenal atresia, jejunal atresia and ileal atresia.

Esophageal Atresia

Esophageal atresia (EA) occurs in 1/3,000-4,500 live births. Approximately one third of infants with esophageal atresia are born prematurely (2). EA occurs as a result of the failure of the primitive foregut to recanalize (3). An overwhelming majority of EAs are accompanied by a fistula between the trachea and the distal esophagus. These tracheoesophageal fistulas (TEF) occur due to the failure of the lung bud to separate from the foregut (3). An EA with a TEF can be distinguished from an EA without a TEF by the presence of a gas in bowel. EA without TEF does not permit any passage of gas into the bowel, but a TEF permits a pathway from the trachea to the distal esophagus and the stomach.

In rare instances, infants have a tracheoesophageal fistula without an esophageal atresia. This is known as an H-type TEF (the connection between the esophagus and trachea looks like an H). It usually presents with recurrent coughing along with aspiration pneumonia. H-type TEF is commonly diagnosed in childhood or sometimes adulthood by esophageal instillation of methylene blue followed by bronchoscopy to look for dye entering the trachea. Once identified, H-type TEFs require surgical correction.

Esophageal atresias should be suspected if any one of the following is present: maternal polyhydramnios (from inability of the fetus to swallow and absorb amniotic fluid); excessive oral secretions in the newborn; cyanosis, choking, regurgitation or coughing occurring with the first feeding. If suspected, the diagnosis of an esophageal atresia can be confirmed by inability to pass the nasogastric tube into the stomach and by a chest radiograph, which shows the coiling of the tube in the proximal esophageal pouch. Injection of 1mL of contrast into the obstructed esophageal segment can also assist with the diagnosis (3).

One half of infants with esophageal atresia have other associated abnormalities. For example, the VACTER association includes vertebral defects, anal atresia, cardiac anomalies, tracheoesophageal fistula with esophageal atresia, radial upper limb hypoplasia and renal defects (2).

Newborns with EA are at risk for pulmonary aspiration, so nasogastric (actually nasoesophageal) suctioning of the esophageal pouch should be implemented once the diagnosis is confirmed. Also, patients should be placed in the prone position to minimize the flow of gastric contents into the lungs (stomach to distal esophagus through the TEF into the lungs). Postoperatively, an esophagogram should be performed before feeding is resumed to determine the integrity of the anastomosis of the two ends of the esophagus. Prognosis is determined by the extent of pulmonary aspiration. Patients with EA commonly have structural malformations of the trachea such as degeneration of elastic, cartilage and connective tissue of the trachea (tracheomalacia). However, tracheal development is normal if the EA presents in the absence of a fistula. Other complications of the disease are failure to thrive, slow feeding, esophageal stenosis, recurrent aspiration pneumonia, reactive airway disease, severe gastroesophageal reflux, coughing and choking (2).

Intestinal Atresias

Intestinal atresias (duodenal, jejunal and ileal) are common and account for approximately one third of all cases of neonatal intestinal obstruction, but colonic atresias are rare. Distribution of atresias within the small intestine is as follows: 50% in the duodenum, 36% in the jejunum and 14% in the ileum. Other congenital abnormalities are more common with duodenal and jejunal atresias as compared to ileal atresia. Atresias affect males and females equally (3).

Duodenal atresia is similar to esophageal atresia in that it also results from a failure of recanalization. In the case of duodenal atresia, the failure occurs after the solid phase of intestinal development during week 4 and 5 of gestation. It may also be caused by local ischemia and may have a genetic component. Duodenal atresia occurs in 1/10,000 live births. Approximately 50% of infants with duodenal atresia are born prematurely (4). Duodenal atresias occur most frequently distal to the ampulla of Vater (3). There are three types of duodenal atresia: Type I is a mucosal web with normal muscular wall. Type II describes a short, fibrous cord that connects two ends of the atretic duodenum. Type III represents complete separation of the atretic ends. Type I is the most common and type III is the least common (5). Other conditions are associated with duodenal atresia: Down syndrome, malrotation, esophageal atresia, annular pancreas, renal anomalies, congenital heart disease and imperforate anus. Bilious vomiting without abdominal distention on the first day of life is the hallmark of duodenal atresia. Other manifestations include polyhydramnios which is present in 50% of cases, jaundice and intolerance to feeding. Radiographically, duodenal atresia is suggested by the presence of the "double-bubble sign" which results from accumulation of gas in the stomach and proximal duodenum. Because of the atresia, bowel gas does not enter the remainder of the bowel until after the first day of life. Duodenal atresia can be diagnosed prenatally by fetal ultrasonography. Initial treatment consists of nasogastric or orogastric decompression in conjunction with IV fluid replacement to correct fluid and electrolyte derangements. Prior to surgical correction of duodenal atresia, an evaluation for associated life-threatening congenital abnormalities should be performed. Duodenal atresia is usually repaired by duodenoduodenostomy which bypasses the obstruction. Long term prognosis is determined by the patient's associated congenital abnormalities (5).

Unlike esophageal and duodenal atresias, jejunal and ileal atresias are not caused by failure to recanalize the intestinal lumen. Instead it is thought that their etiology is an intrauterine ischemic event of the bowel such as intussusception, volvulus, malrotation, arterial occlusion, internal hernia or strangulation due to an abdominal wall defect such as an omphalocele or in gastroschisis (5). This may result in a focal infarction resulting in an atretic portion of bowel. These atresias are also associated with meconium ileus which occurs in

newborns with cystic fibrosis. Similarly to other atresias, a quarter of patients with jejunoileal atresia have a history of polyhydramnios (4).

Jejunal atresias are more common than ileal atresias (5). Isolated jejunal atresia has a higher prevalence in twins and infants with low birth weight. Also, patients with isolated jejunal atresia are more likely to have other unrelated congenital abnormalities (3). There are four different types of jejunal and ileal atresias. Type I is mucosal obstruction that is caused by an epithelial intraluminal membrane, but the proximal and distal ends of the bowel are intact. In type I, which accounts for 20% of jejunal and ileal atresias, the bowel wall and the mesentery of the intraluminal membrane are both intact. Type II is characterized by the connection of the blind ends of the bowel by a fibrous cord and constitutes 35% of intestinal atresias. Type III is subdivided into Type IIIa and IIIb. In type IIIa, the blind ends of the bowel are completely separated by a mesenteric defect that is V-shaped. It accounts for 35% of all atresias. Type IIIb, also known as "apple peel" or "Christmas tree" deformity, describes a loss of the normal blood supply to the distal bowel and is associated with a significant mesenteric defect. It appears that there is a genetic predisposition to Type IIIb (3,5). Type IV comprises 5% of all bowel atresias and is characterized by multiple bowel atresias which resemble a string of sausages (4,5).

Jejunoileal atresia can be diagnosed by prenatal ultrasound. The majority of newborns with jejunoileal atresia exhibit clinical symptoms during the first day of life. Symptoms are characterized by abdominal distention, bilious emesis or bilious gastric aspirate. Other symptoms include jaundice and failure to pass meconium. However, the passage of meconium does not rule out intestinal atresia because a third of infants with jejunoileal atresia will pass meconium prior to development of obstructive symptoms (3). Air-fluid levels or peritoneal calcifications may be seen on plain abdominal radiographs. In the differential of jejunoileal atresia are: Hirschsprung's disease, meconium ileus and meconium plug. These diseases can be distinguished from jejunoileal atresia by contrast studies of the upper and lower bowel which will pinpoint the level of obstruction (4). Definitive treatment requires resection of the atretic portion of the bowel with an end-to-end anastomosis. Postoperatively, nutritional support is provided by parenteral hyperalimentation until bowel function is restored (5). Prognosis is determined by the length and function of the remaining bowel. Long-term complications include malabsorption, feeding intolerance and bacterial overgrowth (3). Multiple atretic segments may result in a short gut syndrome with insufficient or marginal total bowel nutrition absorptive capacity.

Intestinal Duplications

Intestinal duplications are rare congenital abnormalities that consist of tubular or spherical structures with gastrointestinal epithelium. These structures are attached to the intestine and are located on the mesenteric border. The lumen of the normal intestine usually is not continuous with that of the duplication. Usually the duplication and the normal intestine share vascular supply and a fraction of the muscular layer. There are three categories of intestinal duplications. The first category is localized duplications. These duplications are most common in the jejunum and the ileum, although they may occur in other areas of the GI tract. Localized duplications are usually tubular or cystic. Their exact etiology is unknown, although it is thought that defects in the recanalization of the intestinal lumen after the solid stage of embryologic development, may contribute to the development of these duplications. The second category is duplications that are associated with spinal cord or vertebral abnormalities such as hemivertebra or anterior spina bifida. A possible cause of these duplications may be the separation of the notochord during embryologic development. The last category is duplication of the colon. This duplication is commonly associated with abnormalities of the genitals or the urinary tract. In general, duplications tend to be symptomatic and present during the first year of life as a palpable mass or they may cause intestinal obstruction, volvulus or intussusception. Other symptoms include vomiting, abdominal pain, constipation, diarrhea and acute GI hemorrhage. Duplications may be diagnosed with ultrasound, MRI or CT of the abdomen. Undiagnosed intestinal duplications may undergo malignant transformation. Definitive treatment includes complete resection of the duplication with an end-to-end anastomosis (3,7).

Microcolon

Microcolon is a rare congenital cause of intestinal obstruction. The microcolon generally results from intrauterine underutilization of the colon, which would include conditions in which intestinal contents are not passed into the colon during gestation. This would include ileal atresia, but this would not include duodenal atresia, because duodenal atresia is in the proximal small bowel, such that the middle and distal small bowel continue to shed epithelial tissue (meconium precursors) distally into the colon during gestation. Microcolon is also part of a megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS). MMIHS is a genetic disorder with an autosomal recessive pattern of inheritance. This syndrome affects primarily female infants. Infants with MMIHS present with bilious vomiting, delayed passage of meconium and abdominal distention. Dilation of the bladder and the small bowel causes abdominal distention. Physical exam reveals thin musculature of the anterior abdominal wall. Diagnosis is confirmed by ultrasound, upper GI contrast study and an enema which shows a nonobstructed microcolon (7,8). This syndrome is usually lethal within the first year of life (9).

Questions

1. The double-bubble sign on plain abdominal radiograph is diagnostic of what kind of atresia?
2. How could you distinguish between an esophageal atresia with tracheoesophageal fistula (TE) from an esophageal atresia without TE fistula?
3. What other abnormalities are associated with an esophageal atresia?
4. How does an esophageal or duodenal atresia differ etiologically from a jejunal or an ileal atresia?
5. What makes undiagnosed intestinal duplication potentially life threatening?

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Answers to questions

1. Duodenal atresia.
2. Esophageal atresia with tracheoesophageal fistula results in a gas within the bowel, esophageal atresia without tracheoesophageal fistula does not.
3. VACTER association; includes vertebral defects, anal atresia, congenital cardiac anomalies, tracheoesophageal fistula with esophageal atresia, radial upper limb hypoplasia and renal defects.
4. Esophageal or duodenal atresias result from failure of the lumen to recanalize. A jejunal or ileal atresia results from an intrauterine ischemic event.
5. Undiagnosed intestinal duplications may cause a bowel obstruction or may undergo malignant transformations in adults.

Chapter X.10. Craniofacial Malformations

Robert L. Peterson, MD

This is a newborn infant male born to a 29 year old G6 P4 A1 mother at 38 weeks gestational age via vaginal delivery with Apgar scores of 8 and 9 at 1 and 5 minutes, who is noted to have complete left cleft lip and palate.

Exam: He is alert and active in no distress. His head shape is normal with a flat anterior fontanelle. There is clefting of the left upper lip, extending across the alveolar ridge and all the way back into the palate. The uvula is cleft (bifid). His eyes and ears are normal. His neck, heart, lungs, abdomen and extremities are normal.

This infant has some difficulties in feeding initially, which resolve upon use of a cleft palate nipple. Weight gain is a bit slow over the first few weeks of life, but it then improves, following the growth chart.

Clefting of the lip and palate is caused by incomplete fusion of the lateral elements in utero. Normally, during embryogenesis, there is migration of the elements from the side to join in the midline. When this process is interrupted, a cleft results. Pressure from the tongue pushes the palatal shelves up into the nose, moving them away from each other, making the palatal cleft wider. Loss of the muscle activity from the lip (because it does not form a complete band) allows the anterior portion of the palate to drift sideways and open the lip cleft. The cleft in the lip can vary in width from a small notch to a complete division all the way into the nose. In a complete cleft, the lip is completely split into two parts, with a resulting division under the nasal opening on one or both sides. In an incomplete cleft, there will still be some lip tissue under the nasal opening; this is known as the nostril sill. Clefts can be unilateral or bilateral. Isolated clefting of the lip does not cause much functional problem, but makes social adaptation of the baby more difficult.

Clefting of the palate also varies in degree. The most mild form involves clefting of the uvula. This can be associated with "submucous" clefting of the soft palate, where there is failure of fusion of the palatal musculature in the midline. Most infants with this aberrant muscle anatomy learn to compensate. Speech develops normally and the clefting goes undetected. When speech is abnormal, the diagnosis is made by observing a lack of fullness in the central soft palate. It looks thinner and paler in the anterior-posterior direction (the "translucent midline raphe"), and gentle pressure with a cotton tipped applicator will confirm that there is only thin mucosal tissue.

Cleft lip and palate is a relatively straightforward diagnosis to make. Usually it is an isolated condition, but, like all congenital defects, it may be associated with other abnormalities due to environmental factors, intrauterine events or genetic syndromes. The most important of these is Pierre Robin sequence (the new name is "sequence" instead of syndrome because all of the associated anomalies can be explained as consequences of the initial event which is a hypoplastic mandible), where poor development of the mandible (micrognathia) leads to a lack of room for the tongue to fit in the mouth. The tongue, then pushes up the palate, and prevents fusion of the two palatal shelves. The child has trouble breathing due to the small oropharynx, and treatment requires early intervention to keep the tongue from obstructing the airway. Other syndromes associated with cleft lip/palate include Treacher-Collins syndrome, and other syndromes of genetic inheritance of the cleft. These are important for genetic counseling of the child and family.

The goals of management are to achieve normal appearance and normal function. The most important functional goal is to achieve normal speech. Timing here is very important, because there is a window for speech development from about 6 months to about 30 months of age. Normal speech cannot develop if the cleft palate is not repaired, because air from the mouth escapes through the nose and prevents normal sound development. Earlier repair of the cleft palate permits better development of normal speech. If repair is delayed, the child will develop speech habits (compensatory articulations) that will have to be "unlearned" later.

The goals of cleft lip repair are: to get a normal looking lip and to restore the continuity of the lip musculature. This is especially important when the cleft is bilateral. In bilateral clefts, the central portion of the lip (prolabium or premaxillary segment) is not attached to the lateral portion of the lip on either side. Thus, it tends to grow outward and away from the lateral segments, which then tend to collapse medially. Attachment of the lip to close the cleft then creates a band of lip tissue which restrains this forward growth of the central portion. In addition, clefting of the lip is almost always associated with abnormal shape and location of the nasal cartilages. This can be

addressed at the time of initial repair, but growth of the cartilage is usually disturbed and final correction will have to be done as a teenager.

Thus, a typical sequence for cleft lip/palate repair is as follows: a) First repair of cleft lip at about 3-6 months of age (when the child is 5 kg or so). b) First stage of cleft palate repair at about 12 months. Additional repair of cleft lip and or palate at 18 months or so. c) If speech is abnormal, possible procedure to correct velo-pharyngeal incompetence. d) Repair of alveolus to permit normal development of adult dentition at the time when adult incisors are beginning to erupt ("mixed dentition") at age 8-10 years. e) Repair of cleft nose deformity as a teenager.

The prognosis for a child with unilateral cleft lip and palate is generally good. They usually learn to take bottle feedings easily with a cleft palate nipple, and learn to control the escape of fluids through the nose. Speech development can sometimes be problematic, requiring speech therapy. Poor function of the muscles of the soft palate can cause blockage of the Eustachian tubes, and frequent ear aches and otitis media.

There are several other, less common syndromes associated with growth abnormalities. There can be failures of growth and union of other facial bones, leading to a variety of rare facial clefting syndromes. Malformation of the branchial arches can also cause malformation patterns, the most common of which is Treacher-Collins syndrome, an autosomal dominant mandibulofacial dysostosis with zygomatic and mandibular hypoplasia and associated orbital anomalies. Down's syndrome is also associated with characteristic facial malformations, although these are mild and of secondary concern.

In addition, there can be problems of growth of the cranial bones, leading to funny shaped skulls. If the suture lines of the skull fuse prematurely (synostosis), then the bones cannot grow at this suture line, and the skull cannot grow in this direction. If the sagittal suture is involved (the most common), the skull cannot grow and separate across this line, so instead the skull becomes long rather than wide (scaphocephaly) in order to accommodate the growing brain. If the metopic (anterior forehead) suture is involved, this leads to trigonocephaly, with narrowing of the distance between the eyes. If both coronal sutures are involved, the head cannot grow in an anterior-posterior direction, and there is compensatory sideways growth leading to a skull that is shallow and broad (brachycephaly). Fusion of the lambdoid sutures causes flattening of the back of the head for similar reasons. Imbalanced or combined suture problems can result in a variety of other plagiocephalies - literally meaning "funny shaped skull". Reshaping of the skull can be accomplished by surgically opening the involved suture.

The brain is usually able to grow normally if only one suture is involved, compensating by increased growth along the other sutures without increase in intracranial pressure. This is more difficult when more than one suture is involved, causing more pressure on the growing brain. In Crouzon's Disease, a cranial synostosis is combined with exorbitism and midface retrusion ("froglike facies") in an autosomal dominant disorder. A similar disorder with hand syndactyly is called Apert's syndrome. Both require extensive surgery for repair.

Questions

1. In the newborn nursery, the mother of a child with a cleft lip and palate typically has a lot of concerns and will ask about the following. What do you tell her?

a. What caused the cleft lip?

b. Was there anything that she did or took in her early pregnancy that could have caused this, before she knew that she was pregnant?

c. What about feeding the baby and can she breast feed?

d. What surgeries the baby will need, and when?

e. If they have another baby, what are the chances that the next baby will have a cleft lip? What about the babies' children?

2. Why do cleft palate children develop more ear aches?

3. Why do cleft palate children have trouble with speech development, and what can be done to minimize this?

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3. Home page of British Cleft lip and palate association, general information: http://www.clapa.com/

4. A general discussion of cleft lip and palate and the surgeries to repair it with diagrams: http://www.plasticsurgery.org/surgery/cleftlp.htm

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7. Discussion and pictures of other craniofacial deformities: http://www.craniofacial.net/

Answers to questions

1a. The clefting is caused by improper migration of the lateral lip segments in utero. This is a complex process, and sometimes it malfunctions.

1b. Probably not, and reassurance is the best treatment as the parents will inevitably feel some guilt. For future pregnancies, good nutrition (especially folic acid) and avoidance of toxins (alcohol, cigarettes, drugs, medications, environmental) are helpful. For further discussion, see http://www.cleft.net/reduce.

1c. The parents will probably need help in learning how to feed their baby, since the baby has less ability to create suction. Making a larger opening in the nipple, and using a broad nipple can help - the baby can get milk by compressing the nipple with the tongue rather than sucking. Breast feeding is possible, but more difficult. For a nice discussion of this, see http://www.samizdat.com/pp2.html

1d. The surgeries involve repair of the lip in the first year, repair of the cleft palate at about age 1, repair of the alveolar cleft at 6-10 years, and repair of the cleft nasal deformity as a teenager, after growth is complete. Each of these may involve one major operation, and perhaps one or more refinement operations if desired.

1e. The incidence of cleft lip in the general population is about 1:750. This approximately doubles for each affected family member, so the next baby would have about a 1:375 chance of having a cleft. For more precise evaluation, consultation with a genetic counselor is recommended.

2. In cleft palate, the muscles of the soft palate (levator palatini) are incorrectly aligned: they cannot cross the midline as they normally do. Thus, contraction of these muscles does not pull on the Eustachian tube to open it up, and the ears remained "plugged", causing serous otitis which then can get infected and cause otitis media.

3. Because of the clefting of the palate, the children cannot build up air pressure in the mouth (the air escapes into the nose). Thus, they cannot properly form the sounds which require increased air pressure (b, p, t, k, g, v, and s). As they try to learn to speak, they substitute other sounds for the ones that they cannot make ("compensatory articulations"). As they get older, it becomes increasingly difficult for them to unlearn these habits, so repair of the cleft palate should be done prior to speech development if possible. In addition, hearing is often slightly impaired, as noted above.

Chapter X.11. Abscesses
Myrna I. Kuo

This is a 4 year old boy who presents to the hospital with a chief complaint of a painful lump in his neck. He has been complaining of progressively worse pain in his ear for the past few days, but now comes to the office because of the development of the neck mass. He has been given acetaminophen for pain relief. He has otherwise been a healthy child and attends pre-school.

Exam: VS T 37.0, P 100, RR 25, BP 100/60, oxygen saturation 99% in room air. He is alert and active, in no distress. He is not toxic and not irritable. Head and eye exam are normal. His right tympanic membrane is bulging and purulent. His left tympanic membrane is normal. His neck exam demonstrates a fluctuant mass on the right side with overlying cellulitis (redness). His mouth exam shows a normal pharynx, mucosa and good dentition. Heart, lung and abdomen exams are normal. He ambulates normally and no neurological deficits are noted. His color and perfusion are good.

A CBC is obtained which shows WBC 12.0, 60% segs, 15% bands. The neck mass is aspirated with an 18 gauge needle for 3 cc's of thick pus. A gram stain of this shows many gram positive cocci. Clindamycin is prescribed and he is seen in follow-up the next day. The culture is positive for Staph aureus. The neck mass continues to enlarge, so he is hospitalized for further management. A surgeon is consulted who performs an incision and drainage. Entry of the abscess cavity reveals thick pus with loculations which does not drain easily so the incision is enlarged and a gauze drain is placed within the cavity. The staph aureus is determined to be methicillin resistant, but sensitive to clindamycin and vancomycin. He is continued on IV clindamycin and he is discharged from the hospital two days later to continue oral clindamycin as an outpatient. The gauze drain is removed three days after the initial incision. The abscess cavity gradually closes and shrinks.

Abscesses are focal collections of purulent material, usually due to bacterial infection, that are contained within a tissue, organ or confined space. Organisms may reach the tissue through various pathways including direct implantation by a foreign object, contiguous spread from an adjacent locus of infection, dissemination via lymphatics or hematogenous routes, and contamination of sterile tissue by normal flora (e.g., perforation of viscera into the abdomen) (1). As an abscess forms, there is an accumulation of necrotic white cells and tissue cells in the center of the abscess surrounded by a layer of preserved neutrophils and a second layer of dilated vessels and fibroblasts. Without spontaneous or surgical drainage, an abscess occasionally resolves slowly after proteolytic digestion of the pus producing a thin, sterile fluid that is resorbed into the bloodstream. Incomplete resorption leaves a cystic loculation within a fibrous wall, where calcium salts sometimes precipitate to form a calcified mass (2). More often, the abscess remains and becomes walled off by a capsule of connective tissue. Risk factors for abscess formation are immunosuppression, the presence of foreign bodies, obstruction to normal drainage of a visceral tract (e.g., respiratory, biliary, or a sweat gland as in acne), areas of low oxygen tension and stasis (e.g., ischemic tissue or hematomas), and trauma (1).

The symptoms associated with abscess formation vary depending on what organ is affected. For superficial or cutaneous and subcutaneous abscesses there is heat, swelling, tenderness, erythema over the affected site, and sometimes fever. Chronic or subacute deep abscesses present more often with local pain, tenderness, and systemic symptoms such as fever, anorexia, weight loss, and fatigue (1). Abscesses can lead to serious complications such as bacteremia, rupture into neighboring tissue, bleeding by erosion into nearby vessels, impaired function of the affected organ or systemic effects. Prompt treatment is generally preferable, but most abscesses are subacute, in that they have often formed over several days or longer. In general, treatment for abscesses is similar regardless of location. For superficial abscesses, incision and drainage with or without antibiotics is indicated. Treatment of a deep-seated abscess consists of drainage and antibiotics active against the responsible bacteria. Without sufficient drainage, antibiotics are ineffective, because the necrotic center of abscesses are not vascularized (i.e., no antibiotic is delivered to organisms within the abscess). Adequate drainage consists of thoroughly removing pus, necrotic tissue, and debris. To prevent reformation of the abscess, loculations (fibrous strands) must be broken and drainage must be permitted to continue. A gauze wick can be used to maintain the patency of the incision site so that fluid within the abscess can continue to drain out of the cavity. Without a wick or drain to keep the cavity open, the incision site will close and fluid will collect within the cavity causing a recurrence of the abscess. Dead space within the cavity can be eliminated by packing with gauze. The leading end of the gauze packing wick is advanced daily to reduce the size of the abscess cavity as it closes. Predisposing conditions, such as obstruction of a duct or the presence of a foreign body, should be corrected or eliminated if possible. Gram stains and cultures followed by susceptibility studies of isolates obtained from the abscess provide a guide to antimicrobial therapy (1).

Each organ is associated with common microbes, with slight differences in pathogenesis and treatment. Some of the more common locations such as brain, lung, liver, neck, pilonidal, and perirectal will be touched upon in this chapter. Additional areas of abscess formation include abdominal, retropharyngeal, peritonsillar, tubo-ovarian, and osteomyelitis Brodie abscesses. These have been covered in other chapters.

NECK

Cervical lymphadenopathy, which is defined as enlargement of the cervical lymph nodes due to viral infection or bacterial infections that drain to lymph nodes, is the most common reason for neck masses in children. Up to 90% of children between the ages of 4 and 8 years can have cervical adenopathy without obvious associated infection or systemic illness. Cervical lymphadenopathy should resolve as the primary infection resolves.

Cervical lymphadenitis, on the other hand, occurs when acute infection is present within the lymph node. Acute bilateral cervical lymphadenitis is often due to viral infection, while acute unilateral cervical lymphadenitis is usually due to bacteria. Cervical lymphadenitis and abscess formation commonly occur in children under 5 years old (3). It often follows an upper respiratory illness, pharyngitis, tonsillitis, or otitis media. The bacteria spread from their initial sites of infection to the lymph nodes in the neck. If not contained by the child's immune system, they multiply within the node and evoke an inflammatory response (3). Up to 80% of cervical lymphadenitis is caused by S. aureus and group A streptococci. Less common organisms include anaerobic bacteria (from periodontal disease), H. influenzae, Yersinia pestis, gram-negative bacilli, Francisella tularensis, Actinomyces, and Mycobacterium (3,4). S. aureus is more likely to form an abscess, whereas group A streptococci usually form a general cellulitis or more commonly, a simple reactive lymphadenitis. Bacterial cervical lymphadenitis presents with firm, tender, and warm lymph nodes. Fever may or may not occur. Treatment includes antibiotics and warm soaks. If left untreated, these nodes may become fluctuant with regional cellulitis (3). Needle aspiration should be done on fluctuant masses, and antibiotic treatment should empirically cover Staph aureus, with subsequent therapy based on culture and sensitivity results. If resolution does not occur after needle aspiration and antibiotics, incision and drainage should be done (3). Some would argue that needle aspiration is merely used as a diagnostic test to determine if an abscess is present. Once an abscess is identified by needle aspiration, then incision and drainage should immediately follow.

SOFT TISSUE

Cutaneous abscesses primarily form as a result of minor trauma to the skin. The bacterium most frequently involved is S. aureus. Normal skin flora is also commonly involved. The presenting signs are a painful, fluctuant mass that is erythematous and indurated with overlying cellulitis. High fevers may indicate systemic infection and should prompt a more in-depth evaluation. Treatment consists of application of local anesthetic, followed by incision and drainage with probing to remove loculations, irrigating the cavity with saline and sometimes packing with gauze. Because abscess drainage is often very painful and local anesthetics do not penetrate necrotic tissue well, general and regional anesthesia may sometimes be preferable. Elliptical incisions are preferred because they keep the wound from prematurely closing. Applying warm compresses twice a day after drainage is usually recommended. Antibiotic treatment is often used, but it is usually unnecessary (1).

Pyomyositis with subsequent skeletal muscle abscess formation is due to S. aureus in greater than 80% of cases. The accumulation of pus is always intramuscular initially and is not secondary to infection of adjacent skin, soft tissue, or bone. It often occurs after a penetrating wound, prolonged vascular insufficiency in an extremity, or a contiguous infection (5). Often termed tropical myositis due to its geographic distribution, pyomyositis can also be found, though less commonly, in temperate climates. Patients present with fever, chills, malaise, and pain and swelling in the muscle involved (usually large skeletal muscles such as the thigh, psoas and buttocks) (6). The pathogenesis of muscle abscess formation is not clear. One hypothesis is that migrating helminth larvae damage tissue, making it susceptible to bacteria of hematogenous origin or carried by the worm. Treatment of the abscess requires surgical drainage and appropriate antibiotic coverage (usually vancomycin, clindamycin or an anti-staphylococcal penicillin). If group A streptococcus is cultured from a smear of the pus, treatment should be switched to penicillin. Continued fever after drainage and antibiotics may indicate other untreated foci of abscess. A complication of pyomyositis is compartment syndrome (especially when in the anterior tibial compartment), which may require additional treatment including additional surgical drainage, fasciotomy, and debridement (5).

BRAIN

Brain abscesses result from direct extension of cranial infections (e.g., osteomyelitis, sinusitis), from penetrating head wounds, or from hematogenous spread (e.g., bacterial endocarditis, bronchiectasis, congenital heart disease with right-to-left shunt, or IV drug abuse) (7). An abscess in the frontal lobe is often caused by extension from sinusitis or orbital cellulitis, whereas abscesses located in the temporal lobe or cerebellum are frequently associated with chronic otitis media and mastoiditis. Abscesses resulting from penetrating injuries tend to be singular and caused by S. aureus, whereas those resulting from septic emboli, congenital heart disease, or meningitis often have several organisms (8). Bacteria frequently involved include: S. aureus, streptococci (viridans, pneumococci, microaerophilic), anaerobic organisms (gram-positive cocci, Bacteroides, Fusobacterium, Prevotella, Actinomyces, Clostridium) and gram-negative aerobic bacilli (enteric rod, Proteus, Pseudomonas, Citrobacter diversus, and Haemophilus). One organism is cultured from the majority of abscesses (70%), two from 20%, and three or more in 10% of cases. Abscesses due to sinusitis often involve anaerobic bacteria. Once the infection extends into the brain parenchyma, it is encapsulated by glial cells and fibroblasts, forming an abscess (7). The abscess results in increased intracranial pressure, causing symptoms similar to tumors such as headache, vomiting, papilledema, seizures, personality changes, focal neurological deficits, and hemiplegia. Brain abscesses are often fatal unless treated. Treatment consists of prompt administration of appropriate antibiotics: penicillin (for streptococci and anaerobes), metronidazole (for bacteroides), a 3rd generation cephalosporin (for Enterobacteriaceae), vancomycin (for S. aureus infection due to cranial trauma or endocarditis) (7). Clindamycin may also be used for anaerobes and synergistic efficacy with other antibiotics. In many cases, aspiration and drainage of brain abscesses are necessary. Response to antibiotics should be followed by serial CT or MRI scans for a minimum of 4 to 8 weeks. The duration of antibiotic treatment is often about 4 to 6 weeks.

LIVER

Hepatic abscesses can be divided into two broad categories, pyogenic and amebic. Pyogenic hepatic abscesses are uncommon in immunocompetent individuals, but can occur in immunocompromised persons (9). Biliary tract disease and obstruction, abdominal infections via the portal vein or contiguous spread, and generalized sepsis are usually responsible. However, in up to one half of cases, no definite cause can be found (10). The right lobe is most often infected. Many bacteria are involved in liver abscesses, most commonly S. aureus, E. coli, Salmonella, Klebsiella, Proteus, Pseudomonas, enterococcus and anaerobic organisms (11). Patients may have either an acute or subacute presentation. Acutely, they may experience high fever and chills, RUQ pain, nausea and vomiting (9). Less commonly, once the abscess is encapsulated, the patient may only manifest dull pain over an enlarged liver which is tender to percussion (9). Jaundice is uncommon. Treatment consists of adequate antibiotic coverage and percutaneous drainage. Triple antibiotic coverage with an

aminoglycoside or third-generation cephalosporin (gram-negative coverage) plus metronidazole or clindamycin for anaerobes and ampicillin (for streptococcal species) should be used (9).

Amebic abscess occurs by fecal-oral transmission of Entamoeba histolytica, usually involving ingestion of contaminated food or water. Amebae reach the liver after invasion of the intestinal mucosa and enter the liver via the portal vein. The acute presentation is similar to pyogenic hepatic abscess (9). Treatment consists of one week of metronidazole. Most patients will recover with metronidazole alone and percutaneous catheter drainage is only required in complicated cases.

LUNG

Lung abscesses are usually due to aspiration (e.g., during coma, obtunded from alcohol or other drugs, CNS disease, general anesthesia), bronchial obstruction, periodontal disease, infection secondary to lung infarction or complications of pneumonia. Many different bacteria are responsible for lung abscess. Lung abscess due to aspiration are typically normal flora of the GI tract (anaerobes) (12). Virulent organisms (e.g., S. aureus), cystic fibrosis, or endotracheal intubation may cause failure of microbial clearance mechanisms resulting in bronchial obstruction and abscess formation (13). Lung abscess caused by periodontal disease contain normal anaerobic nasopharyngeal flora. Pneumonia due to Klebsiella, S. aureus, Actinomyces, beta-hemolytic streptococcus, Streptococcus milleri (and other aerobic or microaerophilic streptococci), Legionella, or Haemophilus influenzae can sometimes be complicated by abscess formation. In immunocompromised hosts, Nocardia, Cryptococcus, Aspergillus, phycomycetes, atypical mycobacteria or gram-negative bacilli should also be considered. Blastomycosis, histoplasmosis, and coccidioidomycosis can cause acute or chronic nonputrid lung abscesses in visitors or residents of endemic areas. Finally, pseudomonas should be considered in hospitalized patients and individuals with cystic fibrosis. Cavitary TB is not considered a lung abscess but should be included in the differential diagnosis (12).

Symptoms of a lung abscess may range from minimal fever, anorexia, and weakness, to symptoms of pneumonia, i.e., malaise, sputum-producing cough, sweats, severe prostration and temperatures of 39 to 40 degrees (102 to 104 degrees F) (12). Unless the abscess is completely encapsulated, about 50% of patients will cough up sputum that is purulent and sometimes blood-streaked. In fact, an abscess may not be suspected until it perforates into a bronchus, causing copious purulent sputum to be expectorated over the next few hours or several days. Putrid sputum is indicative of anaerobic bacteria. Chest pain suggests involvement of the pleura. Signs of a subacute or chronic abscess are months of low-grade fever, cough, weight loss and anemia (12,13). Treatment usually consists of 1 to 3 months of the following antibiotic treatments: a) clindamycin, b) penicillin with oral metronidazole, or c) antibiotics determined by sensitivity testing. Vancomycin should be added if S. aureus is suspected. Drainage by aspiration or surgery is usually not required for a lung abscess. Postural drainage may be helpful, but should be done with caution. The risk of perforation and spilling of abscess contents is potentially disastrous and unnecessary, as antibiotic treatment will usually suffice. If, however, the abscess is resistant to drugs, segmental resection or lobectomy is indicated.

PILONIDAL

Pilonidal abscesses usually occur in hirsute, adolescents. Pilonidal sinuses are common malformations in the sacrococcygeal area that may occur during embryogenesis. They are lined by stratified squamous epithelium and often asymptomatic; however, hair obstructing the sinus can lead to pilonidal cyst formation. Recurrent infection of a cyst, due to foreign body (ingrown hair) granuloma formation, often leads to pilonidal abscess. Due to its location, cultures of pilonidal abscess predominantly contain anaerobic GI flora. Common symptoms include back pain with local tenderness and induration. The abscess, however, may not be superficially obvious. Smaller abscesses only require incision and drainage, which may be done on an outpatient basis under local anesthesia. All hair and pus should be removed, and the lesion should be packed. The area should be repacked every 2 to 4 days and may take weeks to heal. The abscess cavity, however, is often large and recurrence is common. Therefore definitive treatment is removal of the cyst, sinus, and all sinus arborizations once the inflammation has passed. Antibiotics are rarely necessary (14).

PERIRECTAL

There are several common locations for perirectal abscess: >45% perianal, 20% ischiorectal, 12% intersphincteric, and 7% pelvirectal (14). Perianal abscesses occur in healthy infants and adults during the fourth decade of life and more frequently in males (>2:1 ratio). Because they are commonly deep lesions, there is considerable morbidity associated with inadequate treatment of perirectal abscesses. An understanding of anal canal anatomy helps clarify the pathophysiology of perirectal abscesses. The mucosa of the anal canal is loosely attached to the muscle wall. At the dentate line, columnar epithelium transitions into squamous epithelium, and there are vertical folds of tissue called the rectal columns of Morgagni. The columns are connected at their distal end by small semilunar folds (anal valves), and under the valves are invaginations called anal crypts. The crypts contain collections of ducts from anal glands, which are mucus-secreting structures that terminate in the area between the internal and external sphincters. Most perirectal infections begin as a result of blockage and subsequent infection of the anal glands. This causes normal host defense mechanisms to break down resulting in invasion and overgrowth by bowel flora. A mixed infection of GI flora usually occurs, with E. coli, Proteus, streptococci, staphylococci, and bacteroides predominating (14). GI fistulas, inflammatory bowel diseases (Crohn's Disease), episiotomies, or any local trauma that contributes to anal gland infection, predisposes an individual to perirectal abscesses (14). Fistula formation is common in infants, resulting in recurrence of the abscess unless the fistula tract is excised surgically.

Signs and symptoms of superficial perirectal abscesses include: throbbing pain (aggravated by sitting, coughing, sneezing, and straining), swelling, induration, tenderness, and a small area of cellulitis in the perianal region. Deeper abscesses may cause systemic, toxic symptoms, but localized pain may be less severe (14,15). Small, well-defined perianal abscesses are the only perirectal infections that should be treated on an outpatient basis. Incision and drainage result in almost immediate relief of pain and resolution of the infection. However, many perianal abscesses are large and deep resulting in greater morbidity.

ABDOMINAL

Intraabdominal abscesses most frequently occur as a result of GI tract perforation or inflammation (i.e., ruptured appendicitis). Therefore mostly GI flora, a combination of aerobic gram-negative bacilli (E. coli and Klebsiella) and anaerobes (Bacteroides fragilis) are involved. Symptoms of abdominal abscess include fever and minimal to severe discomfort in the area of the abscess. Anorexia, nausea, vomiting, diarrhea, constipation, and paralytic ileus may also occur. Treatment involves: 1) drainage by surgery or percutaneous catheters, and 2) antibiotics which cover all relevant organisms. Treatment regimens include: a) an aminoglycoside (gentamicin) and clindamycin, b) 3rd-generation cephalosporin and metronidazole, or c) single agent cefoxitin or cefotetan. Hospital acquired infections should also cover Pseudomonas (1).

Questions

1. True/False: Some abscesses can resolve spontaneously.
2. What is the most common organism involved in abscess formation?
3. True/False: All abscesses are treated by incision and drainage.
4. What is the rationale behind multi-drug antibiotic treatment?
5. Does a person have to be immunocompromised to develop an abscess?
6. What are the complications of untreated abscesses?

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Answers to questions

1. True
2. Staph aureus
3. False, lung abscesses are not.
4. Abscesses are often mixed infections, therefore antibiotic treatment needs to provide adequate coverage of the common bacteria associated with that type of abscess. Some antibiotics (notably clindamycin) may provide synergistic efficacy as well.
5. No
6. Bacteremia, rupture into neighboring tissue, bleeding by erosion into nearby vessels, impaired function of the affected organ or systemic effects such as cachexia and anorexia.

Chapter X.12. Lymphangiomas
John J. Chung, MS, MPH

This newborn male infant was born to a 30 year old G1P1 mother at 40 weeks gestation via cesarean section. Prenatal ultrasonography performed at 32 weeks gestation revealed a 1 cm x 1 cm x 1 cm hypoechoic but nonseptated mass in the posterior neck. An encephalocele or meningocele were deemed unlikely and the infant was suspected of having a cystic hygroma (a type of lymphatic malformation). No evidence of fetal hydrops or other congenital anomalies were noted. The pregnancy is closely monitored with detailed serial ultrasounds for the duration of the pregnancy. At term, the hypoechoic lesion is 2 cm x 1 cm x 2 cm. While there is still no indication of hydrops fetalis by ultrasonography, a cervical cystic mass could obstruct a vaginal delivery and the mother is advised to undergo a cesarean section.

Upon delivery, Apgar scores are 8 and 9 at 1 and 5 minutes. VS T 37.5, HR 110, R 60, BP 51/25, weight 3.3 kg (50th %ile), length 51cm (50th %ile). His head is normocephalic with no evidence of additional cystic masses. Eyes, ears, nose and mouth are all normal. A 2 cm wide mass is noted in the posterior neck. Heart, lung, abdomen, extremity, skin and neurologic examinations are normal.

He begins to breast feed normally. Imaging studies fail to demonstrate any other cysts. Because nuchal cysts can grow to obstruct the trachea or esophagus, most of the cyst is surgically excised. Histology of the cyst shows only lymphatic tissue, confirming the diagnosis of a cystic hygroma. Because of its proximity to nerves, the cystic hygroma tissue could not be completely removed. By 12 months of age, local recurrence of the cystic hygroma is evident. Options for recurrent and unresectable lymphangiomas, such as drug sclerotherapy, were discussed with his parents. They are also informed of the possibilities of infection, hemorrhage, and continual recurrence despite treatment.

Lymphangiomas or lymphatic malformations (LM) are defined as isolated regions of lymphatic tissue which are thought to occur after the 6th week of gestation, when developing lymphatic tissue fails to properly anastomose (1,2,3). Lymphatic tissue can also improperly anastomose with capillaries, veins, and arteries (4). These isolated regions of lymphatic tissue function to absorb interstitial fluid and enlarge as lymph fluid continues to accumulate with time (3). Depending on their location and size, lymphatic malformations can be benign and asymptomatic or they can press against nerves, organs, or obstruct circulation (4). For example, lymphangiomas in the head and neck can cause airway obstruction, and alter speech and/or mastication (3).

The true incidence rate for lymphatic malformations is uncertain, since small ones may not be very evident. The most common lymphatic malformation, cystic hygromas, have an estimated incidence of 1:875 among miscarriages (3). By comparison, hemangiomas are much more common and occur in as many as 10% of 1 year olds (5). Lymphatic malformations are found equally in boys and girls (5). Lymphatic malformations are commonly diagnosed in infancy with more than half of the cases identified prenatally or postpartum and more than 90% diagnosed by the 2nd or 3rd year of life (4,6). Lymphatic malformations rarely regress after birth but can remain asymptomatic until later in life when trauma or infections can cause lymphatic malformations to rapidly grow and interfere with other structures (7).

Seventy-five percent of lymphatic malformations are found in the head and neck but lymphatic malformations can occur anywhere (1). Generally, the most common sites are in the head and neck, mediastinum, axilla, and abdomen (1). Lymphangiomas that are microcystic superficial lesions of the skin or mucous membranes have many names: lymphangioma simplex, lymphangioma circumscriptum, capillary lymphangioma and angiokeratoma circumscriptum (4,9). Deeper lymphangiomas can be either microcystic (cavernous lymphangiomas), macrocystic (lymphangioma cystoides, cystic hygromas, or cystic lymphangiomas), or mixed microcystic-macrocystic (4,9).

The etiology of lymphangiomas is unknown (10). However, cystic hygromas have been found to be associated with chromosomal abnormalities such as Turner syndrome and Down syndrome (2,3). Chromosomal abnormalities are usually associated with other congenital findings such as mental or developmental retardation, heart defects, or alterations in the development of sexual characteristics at puberty.

Diagnosis is principally made on the basis of clinical appearance and imaging. For example, capillary lymphangiomas or lymphangioma simplex are superficial white, purple, or red papules that appear wart-like (9). Such superficial lymphangiomas are usually asymptomatic but can become infected. They can occasionally bleed when the superficial lymphangioma is in communication with ruptured blood vessels. Lymphangioma circumscriptum are superficial clusters of papules that are said to look like frog eggs (9). Lymphangioma circumscriptum is also found in skin or mucous membrane but extend deeper into the dermis than lymphangioma simplex (9). Cavernous lymphangiomas usually involve the skin or mucous membranes but they extend deeper into muscle where they form small, thin-walled, lymph fluid filled spaces referred to as microcysts (9).

Cystic lymphangiomas or cystic hygromas are large, well-circumscribed, loculated, lymph fluid-filled spaces (macrocysts) (3,9). Large loculated cysts tend to occur in areas where expansion is possible such as the deep lymph vessels in the neck and head or near other organs. These deep lymphangiomas can be asymptomatic or they can present with signs and symptoms associated with serious complications. Cystic hygromas, usually identified prenatally or antenatally, are especially serious. Considerable lymphedema can accompany growing cystic hygromas which can sometimes lead to hydrops fetalis and intrauterine fetal demise (IUFD) or early perinatal neonatal death (early PND) due to circulatory failure (3). Additionally, the size and position of the cyst may complicate vaginal delivery (3).

When aspirated, the cystic space fluid includes proteinaceous fluid with few lymphocytes (1). MRI findings are important in distinguishing between lymphangiomas and other vascular malformations (1). Arterial or venous vascular malformations enhance with contrast during MRI contrast studies, while lymphatic malformations do not. CT scans can also help differentiate venous malformations from lymphangiomas as well as help identify hemorrhages. Plain film radiographs can identify associated skeletal deformities. Ultrasound imaging is particularly useful during the perinatal/neonatal period (4).

Specimen biopsies of superficial lesions show typical lymphatic vessels lined by well differentiated, flat, endothelial cells (3,8). Deeper lesions show dilated and interconnected lymph vessels that can form loculations (3).

The differential diagnosis includes lymphadenitis, other congenital vascular malformations (hemangiomas, branchial cleft cyst, cellulitis, dermoid cyst), and tumors. Bloody lymphangiomas are often easily confused with hemangiomas or Kaposi's sarcoma (4). Because of the variable location of lymphangiomas, the differential diagnosis should also include site-specific pathologies. For example, the differential diagnosis of a nuchal cystic hygroma should include encephalocele or meningocele, and tumors of the head and neck (3).

Small superficial lymphangiomas are generally left untreated if asymptomatic (1). Cystic hygromas identified in a fetus are especially concerning. The fetus is assessed for additional abnormalities that would increase the risk of fetal death or poor postpartum prognosis such as chromosomal abnormalities, hydrops fetalis, and large cyst volumes (2). These factors are important in whether or not the fetus is aborted or delivered vaginally or by cesarean section. In the U.S., deep lymphangiomas such as cystic hygromas and larger superficial lymphangiomas are surgically excised (1,3,6). However, surgical excision is difficult because of the delicate nature of thin-walled lymphatic tissue and the close proximity of lymphatic malformations to nerves, organs, and blood vessels (3,6). As a consequence, complete excision is possible in less than a third of the cases (6). Incomplete excision does eliminate the space occupying effects of the lesion but are complicated by a high risk of recurrence and infection (3).

In sclerotherapy, drugs including bleomycin, OK-432 (derivative of low virulence Group A streptococcus pyogenes), and fibrin adhesives are used to stimulate sclerosis and regression (6). In the U.S,. sclerotherapy is generally reserved for recurrent or unresectable lymphangiomas but, in some small studies, sclerotherapy agents have been used in place of surgical excision with good results (3,6). Sclerotherapy complications include ulcers, scarring, and recurrence of lymphangiomas (3,7). Other treatment options include interferon-alpha treatment (7), laser ablation or radiation treatment. Radiation treatment carries a number of complications and is usually reserved as a treatment of last resort (7).

Questions

1. Which of the following is NOT a kind of lymphangioma?
    a. lymphangioma simplex or circumscriptum
    b. capillary lymphangioma
    c. cavernous lymphangioma
    d. cystic hygroma
    e. subdural hygroma

2. Which two of the following choices are NOT characteristic of cystic hygromas?
    a. bluish color
    b. increases in size with dependent position
    c. if superficial, transilluminates brightly
    d. does not enhance with contrast in MRI
    e. large neck mass presenting at birth

3. True/False: The differential for a lymphatic malformation depends on its location.

4. In the U.S., primary treatment of lymphatic malformations can include all of the following EXCEPT:
    a. surgical excision
    b. no treatment if benign
    c. pharmacological sclerotherapy
    d. radiation therapy

5. Complications of cystic hygromas in the head and neck include all of the following EXCEPT:
    a. airway obstruction
    b. esophageal obstruction
    c. infection
    d. hydrops fetalis
    e. hemorrhage
    f. no exceptions (all above are correct)

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Answers to questions

1.e. A subdural hygroma is liquefaction of a subdural hematoma.
2.a & b. These are indicative of venous malformations.
3.true
4.d. Radiation is reserved as a last resort.
5.f

Chapter XI.1. Anemia
Darryl W. Glaser, MD

A 22 month old boy presents to your office with a chief complaint of pallor. A visiting relative who has not seen the child for 5 months told his mother that the boy appears pale. The mother brings him in for a checkup even though she notices no change in his coloring (he has always been fair skinned). On review of symptoms you find that he is an active toddler, with no recent fatigue, exercise intolerance, or increase in sleeping. He has had no blood in his diapers and no black or tarry stools. He is a picky eater, taking small amounts of chicken, pork and some vegetables, but loves milk and drinks six to eight bottles of whole milk per day.

Family history reveals a distant aunt who had anemia when she was pregnant but which subsequently resolved. There is no history of splenectomy, gall stones at an early age, or other anemia in the family.

Exam: VS: T 37.5, BP 90/52, P 145, RR 16, Height 85.5 cm (50th %ile), Weight 13.2 kg (75th %ile). General appearance: He is a pale appearing, active toddler, holding a bottle, tearing and eating paper from your exam table. Eyes: No scleral icterus. Pale conjunctiva. Mouth: Dental caries. Chest: Clear. Heart: Mild tachycardia as above, grade II/VI systolic ejection murmur heard best over the upper left sternal border. Abdomen: No hepatosplenomegaly. Rectal: Dark brown, soft stool, negative for occult blood.

CBC: WBC 6,100, Hgb 6.2 g/dl, Hct 19.8%, Plt 589,000, MCV 54 fL, RDW 17%. Reticulocyte count is 1.8%. The lab reports microcytosis, hypochromia, mild anisocytosis and polychromasia. There is no basophilic stippling.

You correctly diagnose iron deficiency anemia, start oral iron and limit his milk intake. You see him in 3 days to assure compliance and his RDW is 27% and his reticulocyte count 17%. When you see him back in two weeks his mother is amazed at his new interest in table foods. His Hgb is now 8.5 g/dl, and his MCV 64 fL. Two months later his hemoglobin has completely normalized, and you continue iron therapy for three more months.

Anemia occurs when the red blood cell mass or hemoglobin content is too low to meet a person's physiologic demands. In children, "normal" levels vary with age, gender, and geographic location (height above sea level). A summary of normal values is listed below (1):

Table 1. Lower limit (3rd %ile) of normal hemoglobin (Hgb column) and lower (3rd %ile) and upper (97th %ile) limit of normal MCV by age and sex (1) (M=males, F=females).

Age	Hgb (g/dl)	Lower MCV limit	Upper MCV limit
1 - 4	11.2	72	85
5 - 7	11.5	75	87
8 - 10	11.8	76	89
12 - 14	12	76	89
15 - 17	12 (F), 13 (M)	78	92
Over 18	12 (F), 14 (M)	80	95

Signs of anemia include pallor of the skin, conjunctiva, and mucus membranes, tachycardia, orthostatic hypotension, heart murmur and edema. Symptoms may include fatigue, headache, dizziness and dyspnea. Other signs and symptoms depend on the cause for anemia, such as jaundice, dark urine, or splenomegaly in hemolytic anemias (2).

When the diagnosis of anemia is suspected based on signs and symptoms, it can quickly be confirmed by laboratory evaluation. The more difficult task is determining the etiology, which can appear daunting due to the myriad of causes of anemia in children. Testing for all these causes at once would be inefficient, time consuming, and expensive. It is, in fact, unnecessary because the differential diagnosis can be narrowed significantly by careful history, thorough examination, and use of various classification schemes.

History

1) Has there been a sudden onset of pallor, fatigue, or exercise intolerance? Rapid onset of symptoms suggests a more acute anemia, while anemia without symptoms may indicate a more chronic process, allowing the body more time to compensate for the low hemoglobin levels. Note that the presence of symptoms does not necessarily reflect the level of anemia. A child whose Hgb drops from 14 to 10 over one week may be quite symptomatic, while the child in our case presentation was virtually asymptomatic dropping to a Hgb of 6.2 over a period of months. Pallor unrecognized by the patient's day to day caretaker also suggests a gradual process.

2) Any history of blood loss? Obtain a menstrual history. Prolonged, heavy periods are a source for acute blood loss. Over time chronic loss can lead to iron deficiency, especially when superimposed on poor dietary iron intake.

3) Did the child have jaundice in the newborn period or episodes of jaundice in the past? Glucose-6-phosphate dehydrogenase deficiency (G6PD) and hereditary spherocytosis will cause recurrent episodes of jaundice and anemia, especially following illness or stress.

4) Describe the child's diet. When did he start whole milk? How much milk does he drink now? Excessive milk intake with inadequate dietary iron is a common cause of iron deficiency anemia in toddlers. Does he eat anything unusual (paper, dirt) or chew on ice? Pica suggests iron deficiency and can predispose to lead poisoning.

5) Has anyone in the family ever had anemia or low blood counts, or ever been on iron? This may suggest a hereditable cause of anemia, but is not diagnostic. A positive response may simply reflect dietary patterns in siblings. It is quite common for families to recall at least one relative who was anemic at some time, especially during pregnancy. Ask if they are still receiving treatment or if the condition resolved. Also remember that a negative family history does not exclude an inherited anemia.

6) Has anyone in the family ever had their spleen taken out or had gallstones at an early age? Surprisingly, not all patients know the reasons for past procedures, or may have been too young when they occurred. A positive response suggests a family history of a hemolytic anemia (such as hereditary spherocytosis). A negative response does not rule out these causes.

7) What is the child's ethnic origin? Hemoglobinopathies (e.g., sickle cell anemia), thalassemias, and G6PD deficiency are more common in certain ethnic groups.

Physical Examination

Compare the child's color to his siblings or both parents. Is he active and playful or fatigued? Tachycardia and heart murmur are common in children with anemia, but look for signs of heart failure including tachypnea, rales, hepatomegaly or edema. Splenomegaly may indicate immune hemolytic anemia or hereditary spherocytosis. Look for any skeletal abnormalities as can be seen with the congenital bone marrow failure syndromes.

Two classification schemes are frequently employed to narrow down the differential diagnosis in anemia. The first uses the MCV to classify the size of the red blood cell as microcytic, normocytic, or macrocytic. Although it can be quite helpful, the system is imperfect. Since MCV values in children vary with age, the age specific MCV values must be used (See Table 1). Even so, certain conditions do not fit neatly into one category. The anemia of inflammation/chronic disease and of lead poisoning can be microcytic or normocytic, and the anemia seen with liver failure can be normocytic or macrocytic.

Microcytic anemias include iron deficiency, thalassemia, chronic inflammation, lead poisoning, and sideroblastic anemia.

Normocytic anemias include acute blood loss, immune hemolytic anemia, hereditary spherocytosis, G6PD deficiency, sickle cell anemia, renal disease, and transient erythroblastopenia of childhood (TEC).

Macrocytic anemias include folate deficiency, B12 deficiency, liver disease, hypothyroidism, neoplasms and bone marrow failure syndromes such as aplastic anemia, Diamond-Blackfan anemia (DBA) and congenital dyserythropoietic anemia (CDEA)

The second classification scheme categorizes anemia by its mechanism. If a patient's hemoglobin is low, it is due to one of three basic reasons: he/she is either not making adequate amounts (decreased production), destroying it (increased destruction), or losing it from somewhere (blood loss). This system is more intuitive and more reliable, but is more difficult to categorize in some cases. A high reticulocyte count indicates that the patient is able to adequately make red cells and is trying to compensate for the anemia, suggesting the cause to be blood loss or destruction. A low reticulocyte count suggests decreased production. Signs of destruction include jaundice, elevated bilirubin, dark urine, splenomegaly, schistocytes and microspherocytes on peripheral smear, and low serum haptoglobin.

Decreased production results from iron, folate, or B-12 deficiency, lead toxicity, thalassemia, aplastic anemia, chronic inflammation, neoplasms, TEC, DBA, renal disease, hypothyroidism, CDEA (congenital dyserythropoietic anemia), and sideroblastic anemia.

Blood loss results from acute hemorrhage, dysfunctional uterine bleeding (heavy and/or prolonged menstrual periods), pulmonary hemosiderosis (pulmonary hemorrhage), Goodpasture's disease, and gastrointestinal blood loss (peptic ulcer disease, other GI conditions).

Increased destruction results from immune hemolytic disease, hereditary spherocytosis, G6PD deficiency, sickle cell disease, thalassemia, DIC (disseminated intravascular coagulation), mechanical heart valves, burns, PNH (paroxysmal nocturnal hemoglobinuria), and hypersplenism.

Iron deficiency is the most common cause of anemia in childhood (2). Prevalence of iron deficiency ranges from 5% to 29% of the population, with higher numbers seen in inner city and socioeconomically deprived populations (3,4). It is most common in toddlers and in the adolescent age groups (periods of rapid growth and higher potential for inadequate dietary iron) (5).

In infants, early introduction (at age 6 or 8 months) of whole cow's milk into the diet is clearly associated with iron deficiency anemia, and patients consuming larger amounts of milk are at higher risk of anemia (3). This is due to three factors: 1) Cow's milk exerts a direct toxic effect on the intestinal mucosa of infants, leading to prolonged microscopic blood loss in the stools. 2) The caloric value of whole cow's milk is high due to fat content, decreasing the appetite and leading to less intake of potential iron-rich foods. 3) The bioavailability of iron in cow's milk is low (6). Accordingly, the American Academy of Pediatrics recommends that cow's milk not be used in the first year of life. Infants should receive breast milk or iron fortified formulas for the first year of life, and iron-fortified cereal should be added at the age of four to six months (6). Infants with appropriate diets and older children and adolescents with iron deficiency anemia must be evaluated for a source of chronic blood loss. Abnormal uterine bleeding and blood loss from the GI tract are common. Blood loss in the urine is rare, and from the lungs (idiopathic pulmonary hemosiderosis) is exceedingly rare. Hemolytic anemias generally do not lead to iron deficiency because the body reuses the freed iron. Iron deficiency has conclusively been linked to behavioral changes (6) and to lower cognitive achievement in school aged children and adolescents (7). Thus it should be recognized early and treated adequately.

Presenting signs and symptoms may be mild because of the gradual onset and the body's ability to compensate for low hemoglobin concentration. Pallor, fatigue, exercise intolerance, headache, or dizziness may be present. Physical exam may reveal pale mucus membranes and skin, especially of the palms, tachycardia with or without heart murmur, and orthostatic hypotension. Laboratory evaluation reveals a low MCV, low hemoglobin and hematocrit, low reticulocyte count, and often an elevated platelet count. The red cell distribution width (RDW), a measure of the difference in size between the smallest and largest RBCs in circulation, may be elevated, denoting a dual population of cells: small (microcytic) iron deficient cells and some normocytic cells with adequate iron. Evaluation of the blood smear reveals microcytosis and hypochromia. Serum iron is low, and total iron binding capacity (TIBC) is elevated with low % saturation. Erythrocyte protoporphyrin is increased. Low serum ferritin is diagnostic of iron deficiency, but normal levels can be misleading because ferritin is an acute phase reactant and can be falsely elevated in inflammation (5). Low-normal ferritin values must be interpreted in light of clues from the history, physical, and other laboratory studies. A bone marrow sample stained for iron shows no iron stores. This test is most definitive, but generally unnecessary and invasive.

Treatment with multivitamins containing iron is inadequate once the child is anemic. Oral ferrous sulfate, available in liquid or pill form, at a dose of 3 mg/kg of elemental iron for mild anemia or 6 mg/kg for severe anemia should be instituted. It should be continued for two to three months after normalization of blood counts to replete the total body iron stores. The liquid can stain the teeth so it should be given in juice rather than dropped directly into the mouth. Avoid giving it with milk as milk interferes with its absorption.

Lead poisoning is less common today with the federally mandated removal of lead from gasoline, canned food sealants, and paint intended for household use in 1977. Since then, there has been a 90% decrease in the number of children defined as "lead intoxicated" (8). Nationwide, 4.4% of children aged one to five meet this criteria with blood levels above 10 mcg/dL (9). The primary source of lead in children's blood today is from lead based paint in older households. Most is ingested as household dust, with only a minor contribution from paint chips (8). Children under 2 years of age are at highest risk due to exploring behavior and the practice of bringing paint dust-coated fingers and toys to the mouth. Not surprisingly, the age and state of disrepair of the home is an important risk factor. Children in an older but well-maintained home have less exposure than those in an old home with cracked and peeling paint (10).

Most lead poisoning is now found through lead screening. The American Academy of Pediatrics recommends that a risk assessment survey be given at health maintenance visits, and if any questions are answered "yes" or "not sure", blood lead levels should be drawn. The survey should be adapted for known lead risks in each community, but should include at least the following three questions (10):

1) Does your child live in or regularly visit a house or childcare facility built before 1950?

2) Does your child live in or regularly visit a house or childcare facility built before 1978 that is being or recently has been renovated or remodeled?

3) Does your child have a sibling or playmate who has or did have lead poisoning?

In communities where more than 27% of housing was built before 1950 or where more than 12% of 1 and 2 year olds have elevated blood lead levels, all children should have lead levels drawn at age 9-12 months and age 2 years (10).

Acute signs and symptoms of lead intoxication are now rarely seen. Vomiting, abdominal pain, and constipation are nonspecific and common in this age group. Because of prevention, screening, and the use of chelating agents as treatment, encephalopathy, seizure, and coma associated with extremely high lead levels are almost unheard of today. Chronic effects of lead poisoning are more ominous, and include possibly permanent behavioral and cognitive deficits, including decrease in IQ points (11,12). Complete blood counts are often normal in children with low to moderately elevated lead levels. Basophilic stippling, seen as fine blue specks in the RBC membrane under light microscopy, can be prominent. Erythrocyte protoporphyrin is elevated (13). Anemia results from lead's inhibition of enzymes required for hemoglobin synthesis (4), but the microcytic anemia of lead poisoning reported in the past is most likely due to concomitant iron deficiency. Iron deficiency leads to pica which increases risk of lead ingestion, and iron deficiency leads to increased absorption and retention of lead from the GI tract.

Treatment depends on the blood lead level (BLL) in mcg/dL (10):

I. BLL <10 requires no action.

II. Levels of 10-20 require education and action to decrease lead exposure, including frequent hand washing, frequent dusting and mopping, and ideally repair or repainting, followed by repeat BLL in 2-3 months.

III. Levels of 20-44 require a detailed history to identify sources of lead exposure, including hobbies (ceramics), vocations (repair of bridges or boats, plumbing, home building/renovating), and contact (car batteries, contaminated soil). Corrective action must be taken to decrease exposure. Consider a home visit or a referral to the local health department for a detailed environmental investigation and referrals for support services.

IV. Levels of 45-69 require all of the above plus initiation of chelation therapy.

V. Levels of 70 or higher require hospital admission for close observation of mental status and immediate IV chelation.

The anemia of inflammation, also called anemia of chronic disease, is the second most common cause of anemia in children after iron deficiency (14). Initially recognized in patients with chronic inflammatory conditions, it has now been shown to occur in the acute setting, accompanying mild self-limiting illnesses such as otitis media or upper respiratory infections (15). The mechanism of anemia is multifactorial, primarily from decreased RBC production (impaired iron utilization and decreased erythropoietin production and response) but also from decreased RBC survival (16). The degree of anemia is usually mild, with hemoglobin concentrations of 10 to 11 g/dl, but can be moderate with hemoglobins of 8 to 9 g/dl. The red blood cells are usually normocytic but can be microcytic (15). Reticulocyte counts are low. Iron studies, if done, show low serum iron, high serum ferritin, and low TIBC. Bone marrow evaluation would show abundant iron stores. Anemia associated with acute inflammation is usually benign and self-limited, resolving 1-2 months after the infection resolves (15). Children with chronic diseases such as rheumatoid arthritis have a more protracted course; even so, the anemia is rarely significant enough to require treatment. High doses of erythropoietin can correct the anemia in those rare cases (14).

Folate and vitamin B12 deficiency are rarely seen in children. They cause a macrocytic anemia which may be accompanied by granulocytopenia and thrombocytopenia. Hypersegmented neutrophils may be seen on peripheral smear of patients with B12 deficiency. The diagnosis is confirmed by low serum concentration of the vitamins (4). B12 deficiency requires a Schilling test to determine the cause of the B12 deficiency (intrinsic factor deficiency, malabsorption due to inflammatory bowel disease, etc.). B12 deficiency is also associated with neuropathic symptoms.

The thalassemias are a group of inherited disorders of hemoglobin synthesis that cause a microcytic anemia. Aberrant hemoglobins have shortened lifespans, so the anemia may be caused by both decreased RBC production and increased destruction. Thalassemia is fully discussed in a separate chapter.

Anemia from bone marrow failure is usually macrocytic. Causes can be congenital (Diamond-Blackfan anemia, congenital dyserythropoietic anemia) or acquired (aplastic anemia, transient erythroblastopenia of childhood). These are discussed in detail in a separate chapter. Replacement of normal bone marrow by malignancy (leukemia or metastatic tumor) can lead to failure of normal red blood cell production, as can restriction of the marrow space by bone in osteopetrosis.

Destruction of red blood cells, or hemolysis, causes release of intracellular contents into the plasma. Consequently, indirect (unconjugated) bilirubin, LDH, and AST (SGOT) may be elevated. The urine may be dark due to excreted hemoglobin or bilirubin. The reticulocyte count is elevated (18). Haptoglobin, a protein that binds free hemoglobin, decreases. A low serum haptoglobin is diagnostic of hemolysis. If the red cells are destroyed in the spleen (extravascular hemolysis) red cell fragments are not seen, and the peripheral smear shows polychromasia and microspherocytes.

Hereditary Spherocytosis (HS) is the most common cause of hemolytic anemia in children. It is inherited in an autosomal dominant pattern in 75% of cases, but family history is not always positive because of variations in severity even among family members. Abnormal membrane proteins cause a loss of portions of the cell membrane, resulting in a rigid red blood cell with a spherical shape. These cells are trapped in the spleen and destroyed, resulting in hemolytic anemia (17). Patients present with jaundice, anemia, and splenomegaly. The reticulocyte count is elevated, and the MCV is normal. An elevated MCHC strongly suggests HS, as it is rarely elevated in any other condition but is high in 50% of those with HS (18). The peripheral smear usually shows spherocytes, but the degree is variable and depends on smear quality. One cannot rule out HS by a lack of spherocytes reported on a peripheral blood smear. The definitive diagnostic test is the incubated osmotic fragility assay, which shows increased hemolysis to osmotic stress.

Patients with HS can have a "hyperhemolytic crisis", which is an acceleration of the rate of hemolysis brought on by infections. They typically present with increased jaundice, pallor, and hemoglobins in the 5-8 g/dl range during or just after a nonspecific viral illness. Blood transfusions may be required. An "aplastic crisis" can occur following infection with human parvovirus B19, the cause of Fifth disease (erythema infectiosum) (18). This virus stops all red cell production in the marrow. The reticulocyte count falls to 0, and in the

face of continued RBC destruction without RBC production, the hemoglobin falls precipitously to levels of 3-6 g/dl. Timely blood transfusions can get these patients through this one time complication. HS patients whose siblings contract Fifth disease must be followed closely. Treatment consists of educating the family about the disease and instructing them to come in for examination and blood work at the first signs of pallor, increased jaundice, or fatigue. Splenectomy is curative but because of the risk of post-splenectomy sepsis, especially in those under age five, the surgery is reserved for those with more severe disease. Indications include frequent hyperhemolytic episodes, symptomatic anemia leading to limitation of lifestyle, gallstones, or growth retardation.

G6PD deficiency is the most common of the RBC enzyme defects. The enzyme deficiency causes the red blood cells to be more sensitive to oxidative stress (17). Hemolysis ensues, resulting in jaundice and anemia. It is an X-linked disorder and so it mostly affects males, but females can be variably affected due to random inactivation of one X chromosome or they can be homozygous (mother is a carrier and father has G6PD deficiency). The clinical course is marked by episodic jaundice. Prolonged neonatal jaundice is sometimes seen. Older patients may have a history of jaundice, pallor and anemia that accompanies infections or certain drugs or foods. Different individuals and different ethnic groups (Asian, African, Mediterranean) may have different mutations which result in differing G6PD deficiency severities, so the patients may have different susceptibilities to severe neonatal jaundice, kernicterus and acute hemolytic reactions. Laboratory evaluation reveals a normocytic anemia with variable evidence of hemolysis such as increased bilirubin, decreased haptoglobin, and hemoglobinuria. The blood smear shows fragmented cells, schistocytes, and may show characteristic "bite" cells or "ghost" cells. Special stains for Heinz bodies, denatured hemoglobin, may be positive. A specific G6PD assay is available, and if low, is diagnostic. The test may be falsely elevated to normal levels during or just after acute hemolysis due to a high reticulocyte count, so it should be repeated several weeks after the hemolytic event if the diagnosis appears likely (18).

Patients can make auto-antibodies against red blood cell antigens due to autoimmune syndromes, medications, infections (EBV, mycoplasma, or nonspecific viruses), or unknown reasons. The presentation is variable, but characteristic findings of hemolytic anemia are the norm. Blood smears show microspherocytes but schistocytes are not seen. The direct Coombs test is positive. Treatment with corticosteroids usually results in resolution of the hemolytic anemia (4,17). Intravenous immune globulin (IVIg) and splenectomy have been used with success in cases refractory to corticosteroids.

Maternal antibodies against infant red blood cell groups can cross the placenta and cause varying degrees of hemolysis (alloimmune hemolytic disease of the newborn). The clinical picture ranges from mild hyperbilirubinemia to hydrops and death, but is most often benign and self-limited. Observation alone or treatment with phototherapy is usually adequate. This topic is covered fully in the newborn hematology chapter.

With intravascular hemolysis, as seen in disseminated intravascular coagulation (DIC), hemolytic-uremic syndrome and burns, mechanical injury to red blood cells causes hemolysis within the blood vessel rather than in the spleen. Red blood cell fragments (schistocytes) are therefore commonly seen on peripheral blood smears (4). Treatment involves correction of the underlying condition. Because the defect is extrinsic to the red cell, transfused blood is hemolyzed as quickly as is the patient's, and so transfusion is only a temporizing measure.

Sickle cell anemia is a hemoglobinopathy common in African, Caribbean, Middle Eastern, and Mediterranean peoples. A mutation in the hemoglobin molecule causes red cells to take on a rigid sickled shape, causing obstruction of flow through the microvasculature. Complications due to tissue hypoxia and hemolytic anemia can be profound. Sickle cell anemia is discussed fully in a separate chapter.

Questions

1. What two classification schemes can be used to narrow down the differential diagnosis of anemia in children?

2. What laboratory finding suggests that an anemia is due to a decreased production of red blood cells?

3. What elements of the history, physical, and laboratory evaluation suggest increased red cell destruction as the cause of anemia?

4. What is the best test to rule in or rule out iron deficiency? Justify your answer.

5. True/False: A child raised in a lead based paint containing home that is well maintained has a significantly lower chance of lead poisoning than if that home is in disrepair.

6. True/False: Cow's milk exerts a direct toxic effect on the intestinal mucosa of some infants, leading to microscopic blood loss and iron deficiency anemia.

7. True/False: Children with iron deficiency anemia caused by excessive cow's milk intake often have a history of black or tarry stools.

8. True/False: The iron content of cow's milk is zero or very close to zero.

9. The lab reports a patient's hemoglobin as 7 g/dl, and the reticulocyte count as 1%. The published normal value for the reticulocyte count is 0.7% to 2.0%, so the reticulocyte count is within the laboratory's normal range. How would you interpret this reticulocyte count?

a. This reticulocyte count is normal, so the patient's bone marrow is making RBCs adequately.

b. This reticulocyte count is low. The laboratory's normal values are incorrect.

c. This reticulocyte count value is normal for a patient with a normal hemoglobin, but for a severely anemic patient, the reticulocyte count should be high. Thus, in view of this patient's severe anemia, this patient's reticulocyte count is actually low and indicative of a condition in which RBCs are not being produced.

d. This reticulocyte count is too high for a low hemoglobin. Thus, this is indicative of a hemolytic etiology.

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Answers to questions

1. Classification by red blood cell size (microcytic, normocytic, and macrocytic anemias) and classification by mechanism (decreased production, increased destruction, and blood loss).
2. Low reticulocyte count.
3. History: dark urine. Physical exam: jaundice, scleral icterus, splenomegaly. Lab: elevated LDH, AST, indirect bilirubin; decreased serum haptoglobin; positive direct antibody test (DAT, also known as Coombs test), high reticulocyte count.
4. Bone marrow stain for iron has the highest positive predictive value and specificity, but it is too invasive in most instances. Low serum ferritin is diagnostic of iron deficiency, but its wide range of normal values and its fluctuation with acute inflammation may make interpretation difficult. Serum iron coupled with TIBC and % iron saturation are satisfactory, but this test is subject to some laboratory fluctuation as well. Response to a therapeutic trial of iron is also acceptable as proof of iron deficiency. No actual correct answer to this question.
5. True
6. True
7. False
8. False. Cow's milk contains a modest amount of iron, but little of it is bioavailable.
9. c

Chapter XI.2. Thalassemia
Kelley A. Woodruff, MD

A 12 month old female of Hawaiian, Chinese, Portuguese and Japanese ethnicity is noted to have a hemoglobin of 9.1 g/dl with an MCV of 58 on a routine CBC screen at her one year well child check up. She is otherwise healthy and has no complaints. PE is normal. On a review of this child's medical record, you note the presence of Hemoglobin Barts on her newborn screen.

Thalassemia is one of the most confusing of the hemoglobinopathies, mostly due to confusing nomenclature, lack of easy diagnostic tests, and its similarity to iron deficiency anemia. Whereas both thalassemia and iron deficiency anemia are characterized by microcytic hypochromic anemias, iron deficiency anemia is easily corrected with iron supplementation, but iron supplementation does not correct the anemia due to thalassemia. In any anemic state, there is increased gut absorption of iron. Even in non-transfused patients, iron overload is often noted in the more severe forms of thalassemia. Since thalassemia is not an iron deficiency problem, it is not be corrected by additional iron. In fact, in thalassemia over time, the body becomes iron overloaded, and iron is "stored" in the organs (liver, endocrine organs and heart), which can cause significant morbidity and mortality.

There are two basic types of thalassemia: alpha thalassemia and beta thalassemia. They have nothing to do with one another. Alpha thalassemia usually results from the deletion of any number of the 4 genes necessary to make alpha globin chains. Occasionally, an alpha globin gene is abnormal instead of being completely deleted. Beta thalassemia usually results from an abnormal gene in one or both of the genes necessary for beta globin chain production. Occasionally, the entire gene (on one allele) is actually deleted. The alpha and beta genes are located on different chromosomes and therefore, abnormalities of each are inherited separately.

Beta thalassemia usually occurs from abnormal beta genes, or less commonly, a deletion of a beta gene. In beta thalassemia, there is a large lack of normal beta chain production, thus causing a relative excess amount of alpha chains, which clump together. This abnormal hemoglobin is very unstable, and leads to erythrocyte death in the bone marrow.

Beta thalassemia minor occurs when only one gene is affected, causing a moderate, lifelong anemia. This typically requires no treatment other than recognition for the purposes of patient education, to avoid supplemental iron, and for genetic counseling.

Beta thalassemia major, historically called Cooley's Anemia, occurs when both genes necessary for beta globin production are affected. Since beta chains are not present in fetal hemoglobin, beta thalassemia does not manifest itself in newborns. Beta thalassemia presents at 6 months of age when adult hemoglobin has replaces fetal hemoglobin. Peripheral anemia, caused by the disease, sends signals to the bone marrow to increase production of erythrocytes (e.g., via erythropoietin), however, erythrocyte production is abnormal (ineffective). This process is called "ineffective erythropoiesis". With time, the marrow cavities (skull bones, facial bones, and ribs) expand, leading to the classical facial features and skull X-ray findings ("hair on end" in untreated patients due to excessive extramedullary hematopoiesis). Erythrocytes that do enter the circulation are noted to be abnormal by the reticuloendothelial system (spleen and liver), and are taken up by these organs with ensuing enormous hepatosplenomegaly. In untreated patients, death usually occurs by the end of the second decade of life from anemia and congestive heart failure.

Currently, part of the standard treatment for beta thalassemia major is lifelong transfusions given every 2-4 weeks. The intent of these transfusions is to keep their hemoglobin trough above 9 or 10 gm/dl. This will, in effect, shut off the patient's own erythropoiesis and stop the vicious cycle of anemia stimulating "ineffective erythropoiesis". With each milliliter of transfused packed red blood cells, the patient receives one milligram of elemental iron. Iron, in addition to being relatively difficult to absorb, is also not easily excreted. Thus, such transfused patients quickly become iron overloaded. Untreated, iron overload will be fatal. Regularly transfused patients need to be on lifelong chelation therapy to help their bodies excrete the excess iron. There are no effective oral iron chelation agents. Currently, most regularly transfused thalassemia patients receive their chelation as a subcutaneous infusion of deferoxamine over 10 hours each night (lifelong). With the combination of transfusion and chelation therapy, life expectancy can to be normal.

A form of alpha thalassemia occurs when any number of the four genes that control alpha globin production are missing, thereby causing an excess of non-alpha globin chains. The various forms of alpha thalassemia with their genetic correlate are listed below:

A. 4 normal alleles (normal)
B. 3 normal / 1 missing gene (silent carrier)
C. 2 normal / 2 missing genes (thal trait)
D. 1 normal / 3 missing genes ("Hemoglobin H disease")
E. 4 missing genes (results in hydrops fetalis)

Silent carriers are 1 missing alpha gene. They have no clinical abnormalities. Their hemoglobin, and hemoglobin electrophoresis are normal and their MCV is borderline normal.

Those with alpha thalassemia trait are clinically normal, but their hemoglobin is slightly low and their hemogram demonstrates microcytic indices. Their hemoglobin electrophoresis is normal unless it is done in the newborn period at which time Hemoglobin Barts is present (recall this finding in the case example at the beginning of the chapter).

Traditionally, people with alpha thalassemia trait are taught that they have a benign condition and no further education is provided. However, it should be emphasized that although the anemia is benign, supplemental iron must be AVOIDED to prevent harmful iron buildup. There is suspected sustained morbidity in persons with thalassemia trait, who are on repeated, or continued iron supplementation. Additionally, such iron supplementation is generally useless, even in menstruating females, as their stores are readily replenished by a greater degree of absorption of dietary iron from the gut. The extra iron is stored in the organs, leading to end organ dysfunction. Additionally, parents with this, so called, "benign" alpha thalassemia trait, can produce offspring with fatal hydrops fetalis if both parents pass on alleles with two defective alpha genes.

The name Hemoglobin H disease is a misnomer. In developed countries with otherwise good medical care, it is not a disease, but rather a condition. People with Hemoglobin H condition can live healthy, long lives. They are not transfusion dependent, as are those with beta thalassemia major. There are some rare variants, such as Hemoglobin H Constant Springs, (the Constant Springs is an abnormal gene, rather than a deletion, named after a U.S. city where it was first identified), that can be dependent on lifelong monthly transfusions. These people are missing 2 genes from one allele, and have the severely dysfunctional Constant Springs gene on the other allele. People with Hemoglobin H need to avoid all forms of supplemental iron, and pregnant women need very close prenatal care for their own health matters. Since the bone marrow of thalassemia patients requires excess folic acid (due to erythroid hyperplasia), most clinicians advise

lifelong supplementation of 1 milligram daily of folic acid to avoid relative folate deficiency. During times of severe illness, or in pregnancy, the hemoglobin may drop significantly below baseline in Hemoglobin H disease, and a transfusion may be recommended. Again, iron is generally not deficient and, thus iron supplementation is not helpful, nor is it appropriate.

When four beta chains clump together, Hemoglobin H is formed. In infants, gamma chains predominate over beta chains, and Hemoglobin Barts (four gamma chains) is formed. Hemoglobin H and Hemoglobin Barts are both useless, with no effective oxygen carrying capacity. There has been a lot of confusion between this abnormal Hemoglobin H (4 beta chains clumped together) and the clinical condition in which 3 alpha genes are missing, called "Hemoglobin H disease or condition". The abnormal Hemoglobin H exists (in varying amounts) in all 4 clinical alpha thalassemia categories. Similarly in newborns, Hemoglobin Barts exists in varying amounts in all alpha thalassemia categories.

Hemoglobin H and Hemoglobin Barts do not cause the degree of ineffective erythropoiesis seen in beta thalassemia. Therefore, the classical "thal facies", "hair on end" skull X-rays, and enormous hepatosplenomegaly, all typical of beta thalassemia, are not seen to such degree in severe alpha thalassemia.

Hemoglobin E results from a single amino acid substitution on the beta globin chains. It is very common in the golden triangle of Laos, Cambodia, and Thailand. In the heterozygous form, it affects one out of three persons in this region. Heterozygous Hemoglobin E by itself is not harmful and causes no anemia. However, when combined with beta thalassemia minor, significant anemia develops over time. Such people usually become transfusion dependent later in the first decade of life, and if treatment is not sought or maintained, early death is most likely. The effects of Hemoglobin E on Hemoglobin H are not clear. Homozygous Hemoglobin E usually causes mild microcytic hypochromic anemia, which resembles alpha thalassemia trait.

Questions

1. In reference to the case presentation at the beginning of the chapter, what is the best approach to an otherwise healthy, asymptomatic 12 month old female with the hemoglobin of 9.1 g/dl (MCV 58) on routine CBC screen and the presence of Hemoglobin Barts on her newborn screen?

a. explain to the parents that the baby may have thalassemia and obtain an electrophoresis.
b. start the baby on Fe supplements and order an electrophoresis.
c. start the baby on Fe supplements, recheck in a month, and if the hemoglobin is not improved then, assume the baby has thalassemia.
d. counsel the family that the baby has a form of alpha thalassemia, and that no immediate other tests or Fe supplements are needed.

2. A 15 year old Filipino female is noted to have a hemoglobin of 10.6 g/dl with an MCV of 65 on routine testing. She reports regular menses lasting 4-5 days each cycle. She has no specific complaints. She is unaware of a family history of anemia. By history, her diet appears to be nutritionally adequate. PE is normal; specifically there is no hepatosplenomegaly, jaundice, or scleral icterus. What is the most appropriate management?

a. start on oral contraceptives and recheck a CBC in two months
b. start on empiric Fe while awaiting results of a hemoglobin electrophoresis and iron studies. Recheck CBC in 2 months if iron was deficient.
c. check for Hemoglobin Barts; if not present start on Fe supplements and recheck CBC in 2 months
d. order a hemoglobin electrophoresis; if Hemoglobin H is not found start on Fe while Fe studies are pending, and recheck CBC in 2 months if iron deficiency anemia was present

3. A newborn Laotian boy is noted to have Hemoglobin E on his newborn screen. He is otherwise well. A family history is not available due to a language barrier. What is the least pertinent issue to be considered here?

a. presence of Hemoglobin Barts
b. hemoglobin at 6 months of age
c. hemoglobin level now
d. the order of the hemoglobins printed on the newborn screen

4. Indicate whether iron supplementation is indicated or contraindicated in each of the following clinical situations.

a. Menstruating female with a hemoglobin of 10.0 g/dl., with no known hemoglobinopathies.
b. Beta thalassemia patient who just lost a modest amount of blood from a scalp laceration. Hemoglobin is 9.5 g/dl.
c. Healthy alpha thalassemia trait male who wants to build up his hemoglobin to run a marathon.
d. Menstruating female with alpha thalassemia trait who has had heavy and prolonged periods for the past year. Her hemoglobin is 8.0 and her iron levels and ferritin demonstrate severe iron deficiency.

5. Some ethnic groups with alpha thalassemia trait have a small risk of hydrops fetalis, but other groups have no risk. How is this possible? (The answer to this question was not stated in the chapter, but it can be answered with exceptionally brilliant thinking.)

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Answers to questions

1. Answer is d. Since the child had Hemoglobin Barts on the newborn screen, a form of alpha thalassemia is present. The hemoglobin of 9.1g/dl implies that it is likely Hemoglobin H thalassemia. There is no need to do a hemoglobin electrophoresis, since the type of thalassemia (alpha) is already known. Additionally, Hemoglobin H is so fast moving that it is typically missed on routine hemoglobin electrophoresis, thereby giving "normal" results. In general, therefore, hemoglobin electrophoresis is typically useless in evaluating for alpha thalassemia. This patient and her family should be provided with genetic counseling and education. She should be counseled to avoid supplemental iron, as a true iron deficiency is extremely rare in Hemoglobin H thalassemia. If iron deficiency is ever suspected, iron studies should be done to clearly document a true deficiency before iron supplementation is started.

2. Answer is b. The two most likely etiologies of the anemia in this young lady are iron deficiency or a form of thalassemia. She could most effectively be managed with a trial of iron (for one month). If a repeat CBC shows no change, then either alpha or beta thalassemia should be considered. A hemoglobin electrophoresis would be the next step if the iron trial fails. An increase in Hemoglobin A2 is very suggestive of beta thalassemia. In this case, the mild anemia would indicate a heterozygous beta thalassemia (beta thalassemia minor). Workup may stop there with proper genetic counseling and patient education. If the hemoglobin electrophoresis is normal, or near normal, then alpha thalassemia is the most likely cause.

3. Answer is C. The effects of Hemoglobin E are most significant when combined with beta thalassemia minor (see text), which is why the newborn's current hemoglobin (mostly fetal hemoglobin with no beta chains) is of the least concern. A CBC should be done at 9 or 12 months of age to screen for coexisting beta thalassemia.

4a. Fe is indicated as a therapeutic trial. But if no improvement in the hemoglobin results, then a thalassemia is possible.

4b. Fe is contraindicated since it will not improve the hemoglobin and it will add to the potential for iron toxicity.

4c. Fe is contraindicated, since it will not improve his hemoglobin and it will add to the potential for iron toxicity.

4d. Despite the presence of thalassemia, iron deficiency is documented by laboratory studies, so iron supplementation is indicated until iron deficiency resolves. Once iron deficiency is no longer present, iron supplements become contraindicated.

5. The four alpha genes are not inherited independently. They are inherited in pairs on each chromosome. Thus, a patient with alpha thal trait who has two defective alpha genes and two normal alpha genes could have this in one of two ways: 1) AX/AX, or 2) AA/XX, where "A" is a normal alpha gene and "X" is a defective alpha gene. Some ethnic groups have the genes arranged in the first form only, in which case, two parents with alpha thal trait would always pass AX to their child resulting in a child with AX/AX (alpha thal trait). Fetal hydrops (XX/XX) could never result from such a genetic arrangement. However, if both parents with alpha thal trait were AA/XX, then their children could either be: AA/AA, AA/XX, or XX/XX (fetal hydrops).

Chapter XI.3. Sickle Cell Disease
Kelley A. Woodruff, MD

A 6 year old girl with sickle cell anemia, who is well known to ED personnel, presents with URI symptoms for 2 days, and fever to 38.9 (102 F). The URI symptoms consist of a stuffy nose, no rhinorrhea, and a dry cough, which has not interrupted her sleep. Oral intake has been decreased, but adequate. She has been given acetaminophen and over the counter cold medications. She also takes daily prophylactic amoxicillin.

Exam: VS T37.7, P 100, R 30, BP 98/52. She is nontoxic appearing. She has anicteric sclera, clear conjunctiva, mild clear white nasal discharge, a non-injected pharynx and normal TMs. No cough is heard during the exam. Her lungs are clear to auscultation. Her heart is regular without murmurs. Her abdomen is soft and non-tender to palpation. Her spleen in not palpated below the left costal margin, and her liver is palpated 2 cm below the right coastal margin. There are no rashes or skin lesions, and she moves all extremities well.

A CBC and blood culture are drawn. She is given IV fluids and IV ceftriaxone. Her primary care physician is contacted to discuss the case and to determine whether she should be hospitalized.

There are over 100 known hemoglobinopathies, but sickle cell disease remains the best described and is the prototype for all hemoglobinopathies. Sickle cell disease is a clinically significant condition which involves the sickle cell gene. Several forms of sickle cell disease exist: sickle cell anemia (the homozygous state, also known as SS disease), Hemoglobin SC disease, sickle beta thalassemia, and other rare entities. The heterozygous sickle cell state results in sickle cell trait. Such individuals are asymptomatic and have no significant medical problems. However, it is important for these individuals to be aware of their trait status for purposes of genetic counseling.

Sickle cell disease carries lifelong health considerations. Historically, 10% of children with sickle cell diseases died before their 10th birthday, most often due to overwhelming infection. Survival and morbidity have been unpredictable, largely due to problems with disease recognition and availability of medical care. Therefore, sickle cell diseases are now identified on the newborn screen in almost all states. This permits a proactive approach to the health maintenance of these patients, resulting in less morbidity and mortality.

The gene mutations for both sickle cell and hemoglobin C disease result in a single amino acid substitution on the beta globin chain. The normal beta globin chain has a glutamic acid in the codon 6 position. A valine substitution here results in hemoglobin S, while a lysine substitution in the same position results in hemoglobin C. Both conditions are autosomal recessive. A single sickle cell gene is carried by about 10% of African Americans and the gene for Hemoglobin C is carried by about 2% of African Americans. Sickle cell disease can be easily detected on hemoglobin electrophoresis. The normal hemoglobin electrophoresis in a person greater than 6 months of age shows about 92.5% Hemoglobin A, which consists of 2 alpha globin chains and 2 beta globin chains, and about 2.5% hemoglobin A2 which consists of 2 alpha chains and 2 delta chains. Since the sickle cell gene produces an abnormal beta globin chain, hemoglobin S is comprised of 2 alpha globin chains and 2 abnormal beta globin chains. In the heterozygous state, the normal beta globin gene produces sufficient beta globin chains to produce enough normal hemoglobin A (asymptomatic heterozygous state). Likewise, hemoglobin C

consists of 2 alpha globin chains and 2 abnormal beta globin chains. Both hemoglobin S and hemoglobin C are also easily picked up on the newborn screen, which utilizes methods that separate out and identify various hemoglobins, abnormal and normal alike. Hemoglobin F (fetal hemoglobin) predominates in the normal newborn, and is completely replaced with hemoglobin A by 6 months of age. Hemoglobin F consists of 2 alpha globin chains and 2 gamma globin chains. Since hemoglobin F has no beta globin chains, it is not affected by the sickle cell gene. The normal adult or child produces less than 1% hemoglobin F. On the newborn screen, hemoglobin S is identified quantitatively at birth in its relation to hemoglobin F. If more hemoglobin S than F is present, the child most likely has sickle cell disease. If more hemoglobin F than S is identified, the child likely has sickle cell trait.

Sickle cell anemia occurs when both alleles of the beta globin gene on chromosome 11 are affected by a single amino acid substitution of valine for glutamic acid (resulting in hemoglobin S). Such children produce no normal hemoglobin A. Instead, they produce hemoglobin S. The presence of hemoglobin S within the red blood cells causes an unnatural stiff folding, or sickling of the red blood cell, especially under conditions of oxidative stress. These sickled cells have a tendency to stack up on one another, and thus causes intravascular clogging in the microvasculature. This in turn leads to a vascular occlusion crisis with infarction of local tissue, and severe pain (vaso-occlusive crisis). Hydration is the mainstay of treatment for such crises. The presence of sickle hemoglobin alone, decreases erythrocyte survival leading to chronic hemolytic anemia. It is always important to know a sickle cell patient's baseline hemoglobin when they are well (while not having an obvious vaso-occlusive crisis). The clinical syndromes as a result of this sickling vary depending on whether one is seeing a pediatric or adult patient.

Sickle cell anemia does not present clinically before 6 months of age because of the protective effect from the uninvolved Hemoglobin F. But after 6 months of age, the usual clinical manifestations include infection (usually respiratory), failure to thrive, unexplained fever, and irritability. Before routine newborn screening for sickle cell disease, young children often presented with dactylitis (hand-foot syndrome), which is a swelling of the dorsum of the hands or feet, associated with pallor and fever. Since appropriate and prompt attention is given to symptoms such as fevers, pain, and swelling without a delay in diagnosis, children presenting with dactylitis from sickle cell anemia has become mostly a thing of the past.

The pediatrician is most often confronted with infectious complications of sickle cell anemia. These children are especially prone to bacterial infections such as pneumococcus, Haemophilus influenzae B and Salmonella. Historically, infections have been the primary cause of death during early childhood. Since fevers alone can increase sickling, any febrile child with sickle cell anemia should be given IV hydration to prevent further sickling, and empiric antibiotic therapy should be strongly considered (after appropriate cultures are taken). One reason for the high rate of infections in children with sickle cell disease is that they are functionally asplenic. Because the spleen acts as a sponge for these abnormal sickled cells, subclinical intermittent episodes of intrasplenic vaso-occlusion occur causing local splenic infarcts. Therefore, by the age of 8 years, sickle cell patients are completely functionally asplenic (due to infarction). All sickle cell patients are given prophylactic penicillin, especially during childhood. Additionally, by now identifying children with sickle cell disease at birth, prophylactic pneumococcal vaccine, plus strict attention to the routine childhood vaccinations have been shown to dramatically decrease childhood morbidity and mortality from infection.

Rarely, infants have massive splenic congestion of red blood cells called the splenic sequestration crisis. When this occurs, it is frequently fatal, since it rapidly removes enormous amounts of red blood cells from the circulation, which can lead to circulatory collapse.

A pain crisis is one of the most common reasons for hospitalizing an older child with sickle cell anemia. In a pain crisis, a specific limb or other body part is affected by the vaso-occlusive effects of the sickling cells in the microvasculature. The biggest challenge to the treating clinician in managing this condition, is to administer sufficient analgesia to stop the pain. This is problematic for a variety of reasons: fear of narcotic addiction on either the family's part or the caregiver's part, belief that the pain cannot be controlled completely, belief that some patients exaggerate their pain, and lack of quick access to appropriate analgesics. Success in treating a painful crisis is reached when the analgesic is effective in stopping the pain. Standard doses of analgesics may not be sufficient. Many painful crises can be managed at home with oral analgesics and oral hydration. However, other such crises require IV hydration and IV narcotic analgesics. In these cases, a continuous infusion of a narcotic such as hydromorphone (Dilaudid) with a PCA (patient controlled analgesia) pump is far superior to a "Q 3 hour prn pain" regimen. Meperidine (Demerol) should never be used because patients receiving this have a higher incidence of seizures. There is presently no role for serial intramuscular analgesic injections for pain management.

Acute chest syndrome is another common reason for hospital admission in the older child. Clinically, this is an acute pneumonia-like illness characterized by fever, dyspnea, chest pain, and fatigue. It is usually caused by local pulmonary infarction from vaso-occlusive sickling. Often, acute chest syndrome is complicated by Mycoplasma pneumonia.

Another unique complication of sickle cell disease is aplastic crisis, especially erythroid aplasia. This is often the direct result of human parvovirus infection. Other complications of sickle cell disease include devastating cerebral strokes, leg ulcers, bone infarction, bone marrow hyperplasia, priapism, gallstones, biliary tract disease, or splenic sequestration crisis in the young child.

Hydration is the mainstay of treatment for vaso-occlusive crises, pain crises, strokes, and infections associated with sickle cell disease. Vigorous intravenous hydration should be given to the very young child (<5 years). Above this age, outpatient oral hydration can be considered for mild complaints only. Intravenous hydration with at least twice maintenance fluids, after deficits are corrected, is mandatory in treating dehydration, and strongly recommended in all other situations.

Prevention of the clinical symptoms associated with sickle cell anemia is not considered a universal goal because, unlike other hemoglobinopathies, the clinical course of each patient is unpredictable. An individual patient can go for years without any significant problems, and then have many crises for months or years. Allogenic bone marrow transplantation (from an unaffected donor) would cure the patient of sickle cell disease, but such a transplant is done most safely in infancy, before one knows what that individual's sickle cell course, and its morbidity, will be. Allogenic transplantation carries its own serious morbidity (graft versus host reaction, immunosuppression, etc.), thus it is impossible to predict the risk/benefit ratio for an individual patient. Bone marrow transplantation in an older child would only be considered in the presence of significant morbidity from sickle cell disease itself. However, at that point, end organ tissue damage has occurred, further increasing the morbidity of transplantation. Thus, allogenic bone marrow transplantation is not a good strategy for sickle cell disease.

It has been shown that patients with sickle cell anemia become clinically asymptomatic if the amount of Hemoglobin S in the circulating blood is less than 30%. One way to accomplish this is to transfuse children with normal red blood cells, thereby diluting down their amount of Hemoglobin S, and also shutting off their own hematopoiesis to a large degree. Thus, children with significant morbidity can be placed on a transfusion protocol, in which patients are transfused about every 2 to 4 weeks, indefinitely. The goal of transfusion therapy is to lower the percentage of hemoglobin S to <30% at all times, and to keep the hematocrit below 46%, reducing blood viscosity. With this, there is no further clinically significant sickling. The main hindrance to a transfusion protocol is iron overload. Without chelation, iron overload is eventually fatal (due to hemochromatosis). Currently, chelation involves nightly 10 hour subcutaneous

infusions of deferoxamine as long as the transfusions continue. Poor compliance is an issue, especially in the teen years. Additionally, alloimmunization to blood products can develop in some patients. This creates greater difficulty in obtaining compatible blood products causing a higher incidence of delayed hemolytic reactions.

Other methods to decrease the relative amount of hemoglobin S are currently under investigation. Such methods are met with only varied individual success. Hydroxyurea has been shown to increase the percentage of Hemoglobin F (which lacks abnormal beta globin and does not sickle), thereby creating a relative decrease of Hemoglobin S. This is an oral medication with few other side effects and would seem to be an attractive therapeutic option. Unfortunately, it has not been shown to be consistently effective in reducing either the frequency or severity of symptoms in these patients.

Children with hemoglobin SC disease have one beta-C mutation on one allele and one beta-S mutation on the other. Hemoglobin SC disease is typically associated with milder and less frequent vaso-occlusive events compared to sickle cell anemia. However, like sickle cell anemia, the clinical course can be quite variable. Typically, patients go for years between clinically significant events. They usually have a higher hematocrit than those with sickle cell disease, as they have a less chronic hemolysis. Children with SC disease should receive the same prophylactic care as those with sickle cell anemia.

Likewise, sickle beta thalassemia, in general, is associated with milder symptoms than sickle cell disease, although the clinical severity depends on the type of beta anomaly present. If the beta gene is deleted, the degree of morbidity is similar to patients with homozygous sickle cell disease. If the beta gene is present but abnormal, then the clinical severity tends to be milder, comparable to SC disease.

Questions

1. Of the following, what is the best approach for a febrile child with sickle cell disease?
   a. CBC, BC, oral hydration, IM or oral antibiotics if source of infection is noted on PE.
   b. CBC, BC, IM ceftriaxone, follow-up with PCP next day.
   c. CBC, BC, admit for IV hydration and IV antibiotics.
   d. CBC, BC, no oral antibiotics if no specific source of infection is noted on PE.

2. A 13 year old girl with sickle cell anemia is admitted to the hospital for treatment of a pain crisis. She states her right arm and shoulder started hurting yesterday evening. She has taken acetaminophen with codeine every 3 hours for the last 8 hours, but the pain has only escalated. She denies recent fevers, cough, or URI symptoms. She is on no routine pain medications at home, and was last admitted 5 months ago with a similar pain crisis. On PE, she is in obvious pain, and is crying. Her exam is remarkable for pallor, and slight scleral icterus. She has full range of motion of the right arm, and the rest of her joints. CBC shows a hemoglobin of 7.9 g/dl, WBC 17.8, and platelet count of 543 thousand. Appropriate initial management includes:
   a. IV hydration if oral intake is insufficient, IV or PO pain management as needed.
   b. IV hydration, hydromorphone PCA plus continuous infusion.
   c. IV hydration, IM meperidine prn.
   d. IV hydration, transfusion of PRBC, IV narcotic q 4 hours prn.

3. Explain why most states have adopted newborn screens that identify sickle cell disease at birth.

4. Explain why children with sickle cell disease do not develop symptoms until after 6 months of age?

5. Will a child with sickle beta thalassemia be identified as such on its newborn screen? Why or why not?

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Answers to questions

1.c. This fever is significant, thus there will be an increase in sickling, and the patient is at risk for vaso-occlusive events. Therefore, IV hydration is necessary. It is also prudent to start empiric antibiotics after blood cultures are obtained.

2.b. Appropriate initial management should include vigorous IV hydration, plus IV pain management to include both a continuous infusion and a PCA. One would not transfuse initially, because a transfusion of packed red blood cells will only increase the viscosity of the blood, causing more sickling. Also, one does not know at this point, what the baseline hemoglobin is. The hemoglobin of 7.9 g/dl may not be very different than baseline. If there is further hemolysis, and a transfusion is indicated, it should be done carefully after several hours of IV hydration. Also, remember that meperidine increases seizure activity in children with sickle cell anemia, and is contraindicated.

3. It has been shown that a proactive approach to sickle cell disease decreases morbidity and mortality. Therefore, by identifying all children with sickle cell disease at birth, before symptoms start (usually after 1 year of age), quality of life can be improved.

4. Only after 6 months of age is gamma globin chain production decreased and beta globin chain production sufficient to cause sickling.

5. No. Both beta and sickle anomalies are on the beta globin gene. The newborn screen will identify the sickle hemoglobin, but will not identify the abnormal beta globin genes. The newborn screen will therefore appear as that for sickle cell trait with Hemoglobins F,A, S.

Chapter XI.4. Bone Marrow Failure
Desiree Medeiros, MD

This 2-1/2 year old male is referred to the pediatric hematologist with a chief complaint of easy bruising, nosebleeds and decreased activity for one week. He has no history of fever or appetite changes. His past medical history is unremarkable. There is no travel history, history of recent illnesses, or known exposure to toxins.

Exam: He is a well developed, well nourished, pale boy in no acute distress. His conjunctivae are pale. Sclera are anicteric. TMs are normal. His oral mucosa is moist and shows rare petechiae on the buccal mucosa. He has some small palpable posterior cervical lymph nodes. He has a sinus tachycardia with a grade I/VI systolic ejection murmur, without a gallop. His lungs are clear to auscultation. His abdomen is soft and nontender with normoactive bowel sounds. He has no palpable masses, hepatosplenomegaly, or inguinal hernias. His penis and testes are normal (no masses). He has no rashes, but he has ecchymoses present on his left shoulder, chin and both lower extremities. Petechiae are present on his extremities and groin.

Labs: Hemoglobin 7.9 g/dl, hematocrit 24%, platelet count 12,000, WBC 3,000 with 90% lymphocytes (absolute neutrophil count 210). Reticulocyte count 0.5%. A bone marrow aspirate and biopsy show a markedly hypocellular marrow (12% cellularity) with decreased megakaryocytes and erythroid and myeloid precursors. Bone marrow cytogenetics are normal. A diepoxybutane test shows no increase in chromosome breakage. Ham's acid serum test is normal. Serology for CMV, EBV, parvovirus, and hepatitis demonstrates no recent infection.

He is diagnosed with severe acquired aplastic anemia. One of his sisters is a perfect 6 out of 6 HLA match and he undergoes a matched related bone marrow transplant.

Bone marrow failure is a decreased production of one or more cell lines (erythrocytes, granulocytes, and/or platelets) in the bone marrow resulting in peripheral blood cytopenia. These disorders can either be inherited or acquired. The inherited cytopenias are due to a genetic abnormality and may be associated with congenital physical anomalies. The acquired cytopenias may be due to exposure to a toxin, infectious agent (however, a causal agent is usually not identified), or invasion of the bone marrow by a neoplastic process.

The most common type of bone marrow failure not due to neoplastic causes, is aplastic anemia. Acquired aplastic anemia results from an injury to the bone marrow by radiation, drugs (chemotherapy, antibiotics, such as chloramphenicol), insecticides, toxins (benzene, carbon tetrachloride), or infection (hepatitis, HIV, CMV, parvovirus) (1). However, most cases of acquired aplastic anemia are without an identifiable cause (idiopathic). The onset of symptoms is gradual. Signs and symptoms include pallor, fatigue, weakness, loss of appetite, easy bruising, petechiae, mucosal hemorrhage, and fever. Laboratory evaluation demonstrates a normocytic or macrocytic anemia, reticulocytopenia, leukopenia, and thrombocytopenia. A bone marrow biopsy is essential to make the diagnosis and typically shows depression or absence of hematopoietic elements with fatty infiltration of the marrow (2). Severe aplastic anemia is defined as pancytopenia with an absolute neutrophil count <500, platelet count <20,000, reticulocyte count <1%, and <25% bone marrow elements on bone marrow biopsy (2,3).

Without treatment, acquired severe aplastic anemia carries a high mortality rate, with deaths occurring within a year of diagnosis. These are usually due to fatal infection or hemorrhage (2). Supportive care (intravenous antibiotics and transfusion support) has improved outcomes. Early stem cell transplantation with an HLA matched donor is the treatment of choice for severe aplastic anemia (1,2). When transplantation is an option, blood product support should be used sparingly to reduce the risk of sensitization and graft rejection. When stem cell transplantation is not feasible, immunosuppressive therapy with high dose corticosteroids, anti-thymocyte globulin and cyclosporin A is an alternative (1,2).

Fanconi's anemia is inherited in an autosomal recessive pattern (4). Classically, patients have pancytopenia and characteristic congenital anomalies. These include hyperpigmentation and/or cafe-au-lait spots on the trunk, neck and intertriginous areas, short stature, upper limb abnormalities, hypogonadism, skeletal anomalies, eye or eyelid changes, renal malformations, and more rarely, deafness, gastrointestinal and cardiopulmonary malformations. Blood counts start to decrease between 4 and 12 years of age. This usually presents with thrombocytopenia followed by neutropenia then anemia. Severe aplastic anemia develops months to years after initial CBC changes. MCV is often >100 fl. Fetal hemoglobin and i-antigen (an antigen on immature red cells) are increased. Macrocytosis, fetal hemoglobin and the i-antigen are manifestations of a stressed bone marrow. Bone marrow shows patchy hypoplasia. The diagnostic test for Fanconi's anemia is a chromosome breakage analysis using clastogenic agents such as diepoxybutane or mitomycin C (1,4). A high proportion of cells will show chromosomal breaks. Children with Fanconi's anemia have a higher incidence of acute leukemia, squamous cell carcinoma, and hepatocellular carcinoma (4). Therapy consists of supportive care with transfusions and/or antibiotics for infection. Some patients respond to corticosteroid and androgen therapy (4). Stem cell transplantation from a matched sibling donor, or from an unrelated donor if a sibling donor is not available, is recommended in patients who are not responsive to corticosteroid and androgen therapy.

Diamond-Blackfan anemia (DBA) or congenital pure red cell aplasia is usually inherited in an autosomal dominant pattern (5). Infants present in the first 3 months of life with pallor and poor feeding. Associated physical anomalies are present in 25% of patients and include short stature, craniofacial abnormalities (hypertelorism, flat nasal bridge, and high or cleft palate), thumb abnormalities, skeletal anomalies, deafness, learning difficulties, and renal and cardiac abnormalities (1,5). CBC reveals a normocytic or macrocytic anemia with reticulocytopenia. White cell and platelet counts are normal. Fetal hemoglobin is elevated on hemoglobin electrophoresis and i-antigen is expressed on RBCs. Erythrocyte adenosine deaminase levels are high. Chromosome studies are normal. Bone marrow is cellular with isolated reduction of red cell precursors (1,5). Corticosteroids remain the mainstay of therapy for DBA. Up to 70% of patients have a good initial response to oral corticosteroids (5). The dose can be individualized according to response. However, about one-half of patient with DBA require chronic transfusions, either because they did not respond to corticosteroids or because they developed significant side effects. Rarely, spontaneous remission occurs. Other therapies, such as erythropoietin, interleukin-3, cyclosporin A, intravenous immune globulin, androgens, or splenectomy have been used but have not shown consistent benefit (5). Stem cell transplantation is potentially curative.

Transient erythroblastopenia of childhood (TEC) is an acquired red cell aplasia which occurs in healthy children between 6 months and 5 years old (5). The onset is usually at an older age than that seen in DBA. These children present with a gradual onset of symptoms of anemia, such as pallor and decreased activity. The physical examination is unremarkable except for pallor and tachycardia. A complete blood count (CBC) shows a normocytic normochromic anemia with hemoglobins ranging from 3 to 8 g/dL (5). The reticulocyte count is extremely low. White blood cell and platelet counts are usually normal. Bone marrow examination is not necessary but reveals erythroid hypoplasia (5). Chemistries, such as LDH, bilirubin, and haptoglobin, are normal. During recovery, the reticulocyte count and RDW rise.

RDW (measurement of the distribution width of red cells) rises when there is a spectrum of older (smaller) and younger (larger) red cells. Spontaneous recovery occurs within weeks to months. Recurrence of TEC is rare. Packed red blood cell transfusion may be necessary in patients who exhibit associated cardiac compromise, but is usually not necessary since the onset of the anemia is gradual (5).

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired disorder characterized by hemolytic anemia, thrombosis and progression to pancytopenia (6). It is rarely seen in the pediatric population but should be considered in any child with anemia and "dark urine". The classic presentation is paroxysmal episodes of hemolysis, hemoglobinuria and abdominal and back pain. Pain is due to intravascular hemolysis or small vessel thrombosis. Diagnosis is confirmed by laboratory testing designed to show RBC sensitivity to complement lysis. The Ham's (acid hemolysis) and sugar-water lysis tests show selective lysis of PNH RBCs (3,6). Therapy is controversial. Corticosteroids seem to decrease hemolysis in adult patients (6). Iron supplementation may be necessary because of significant daily iron losses. However, it is thought to exacerbate hemolysis (6). Long term anticoagulation to prevent thrombosis may be required. Stem cell transplantation may play a role in patients with markedly hypoplastic marrows.

Dyskeratosis congenita is a rare X-linked recessive disorder characterized by the triad of: 1) hyperpigmentation of the face, neck and shoulders, 2) mucous membrane leukoplakia, and 3) dystrophic nails (3). Approximately 50% of patients will develop refractory pancytopenia and severe bone marrow hypoplasia. They are also at risk of developing acute myeloid leukemia (3). Stem cell transplantation is an effective therapy.

Thrombocytopenia with absent radii (TAR) is usually diagnosed at birth because of the characteristic physical finding of bilateral absence of the radii and presence of thumbs. These infants also present with petechiae and bloody stools. Associated problems include additional bony deformities, facial hemangiomas, congenital heart disease, and cow's milk allergy (1,7). The platelet count is typically below 50,000 at diagnosis (1,7). Bone marrow studies demonstrate markedly decreased or absent megakaryocytes and normal erythroid and myeloid cell lines. TAR has an autosomal recessive inheritance pattern. The risk of hemorrhage is greatest in the first year of life with mortality being due to intracranial or gastrointestinal hemorrhage (1). Therapy includes platelet support for bleeding symptoms and as prophylaxis for infants with severe symptomatic thrombocytopenia. Dietary modifications are required for those with cow's milk allergy. The prognosis for patients with TAR is very good. After the first year of life, the platelet count rises to above 100,000 which is adequate for necessary orthopedic intervention (1).

Bone marrow infiltration due to leukemia or diseases metastatic to the bone marrow potentially results in pancytopenia by crowding out the normal bone marrow elements. Patients will often first present with symptoms related to the suppression of one or more of the cell lines (RBCs, WBCs, or platelets). Patients present with lethargy (from anemia), bruising and bleeding (from thrombocytopenia) and/or unexplained fever. They may also complain of bone pain or present with a limp. A CBC shows pancytopenia or anemia, thrombocytopenia and leukocytosis. Depending on the underlying malignancy, the physical examination, and laboratory or radiographic studies will demonstrate other abnormalities.

Questions

1. What is the treatment of choice for severe acquired aplastic anemia?
2. What laboratory study is diagnostic for Fanconi's anemia?
3. How can one differentiate between Diamond Blackfan anemia and transient erythroblastopenia of childhood?
4. What is the triad associated with dyskeratosis congenita?
5. Which two factors are associated with gastrointestinal hemorrhage in infants with TAR syndrome?
6. Name some viruses and drugs which cause aplastic anemia?
7. What is the i-antigen and what hematologic problems is it associated with?

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Answers to questions

1. Stem cell transplantation from a matched sibling donor or other compatible stem cell source.
2. Diepoxybutane induced chromosome breakage (increased in patient with Fanconi's anemia).
3. Diamond Blackfan anemia presents at an earlier age (<1 year) and may have associated physical anomalies. At diagnosis, MCV, hemoglobin F and i-antigen are increased. TEC presents at an older age (>1 year). Since it is acquired, there are no associated anomalies. MCV, hemoglobin F and i-antigen should be normal.
4. Skin hyperpigmentation, mucous membrane leukoplakia, dystrophic nails.
5. Cow's milk allergy and thrombocytopenia.
6. Viruses: hepatitis, HIV and parvovirus. Drugs: Chemotherapy, chloramphenicol.
7. The i-antigen is a marker found on immature red cells. It, along with fetal hemoglobin and macrocytosis are manifestations of the fetal-like hematopoiesis seen in the stressed bone marrows of patients with acquired aplastic anemia, Fanconi's anemia, and Diamond Blackfan anemia.

Chapter XI.5. Newborn Hematology
Robert W. Wilkinson, MD

This is a newborn female born to a 17 year old gravida 1, para 0, B+, mother at 39 weeks gestation. Maternal risk factors include a kidney infection in the second trimester. All other risk factors are negative. After an uneventful vaginal delivery, the infant is discharged at two days of life breast feeding at home. On the third day of life, moderate jaundice is noted and a bilirubin in the primary care doctor's office is 18. Home phototherapy is started, but on day six, the bilirubin is 22.9 with the direct component of 0.4. She is hospitalized for inpatient phototherapy. Her hemoglobin was 15.7 earlier, and it has now dropped to 13.4. The bilirubin continues to rise to 25.6 in spite of phototherapy. A G6PD is normal and the reticulocyte count is 3.1. Stools are negative for occult blood. The blood smear shows moderate aniso and poikilocytosis.

She is transferred to a tertiary pediatric center where she is noted to be normal except for marked jaundice. Her mother is of German decent and her father is Caucasian and Puerto Rican. Her mother was treated for newborn jaundice due to presumed ABO incompatibility. Others in her family also had neonatal jaundice. The father's history is unremarkable. No other family member had neonatal jaundice or anemia or gallstones.

Upon admission, vital signs are normal. She is visibly jaundiced and a spleen tip is palpable. Labs show a bilirubin of 25, white count of 17.5, platelets of 230,000 and an unremarkable differential. The hemoglobin is now down to 10.7 in spite of a reticulocyte count of 4%. In addition, the smear now shows moderate schistocytes with burr cells and moderate spherocytes. Blood type is B+ and the Coombs is negative. She is transfused and phototherapy continues until the bilirubin falls to 12. The infant has an otherwise uneventful course in the hospital and the final diagnosis is hyperbilirubinemia and anemia due to hereditary spherocytosis. In addition, alpha thalassemia trait is found on her newborn screen. Incubated red cell osmotic fragility studies on the mother and other maternal family member are consistent with hereditary spherocytosis.

At the moment of birth, the physician can be confronted with complex hematologic problems seen at no other time in life. Newborn red cells are much different than in older children and white cell and platelet disorders can be quite unique. Coagulation factors are abnormal and hemostasis can be markedly altered. Normal values for most newborn blood tests are different compared to children and adults. Interpretation of results in term and premature newborns can be critical.

Significant red cell disorders in the newborn period may be associated with a family history of anemia, jaundice, falling hemoglobin and reticulocytosis in addition to abnormal RBC morphology. The presence of surface antibodies (e.g., anti-A and/or anti-B) may be helpful or the deficiency of intraerythrocytic enzymes (e.g., G6PD deficiency). Finally hemoglobinopathies and thalassemia may offer an almost infinite combination of symptoms and signs in the newborn. Virtually all red cell problems are isolated and the rest of the hemogram is normal. Marrow failure resulting in pancytopenia with associated infections and altered hemostasis is vary rare. Definitive studies on red cells can be delayed for three months when the infant is well and their blood volume is larger. As in the above case, studies of maternal family members subsequently confirmed the diagnosis of hereditary spherocytosis. It is important to remember that in the perinatal period (28 weeks gestation to 28 days after birth) there are normal physiologic changes occurring in red cells. Some of these changes include switching from fetal to adult hemoglobin production, a 30% drop in hemoglobin, a fall in mean red cell volume (MCV) as well as changes in membrane pliability and intracellular enzyme levels. RBC survival is further impacted by acquired infections, medications, and other high-risk conditions. Repeated monitoring of hemoglobin and reticulocyte counts is warranted in the sick and unstable newborn.

Hydrops fetalis results from severe intrauterine hemolysis and anemia necessitating emergency exchange transfusion. The cause is usually due to severe alpha thalassemia, red cell surface antibodies or congenital infections. Rh incompatibility usually presents with rapid hemolysis and varying degrees of anemia and jaundice (depending on the extent of maternal sensitization and antibody production).

White blood cell abnormalities may be asymptomatic and incidental or associated with fever, infection, and altered host resistance. Wide fluctuation in the WBC count can be noted depending on marrow production of granulocytes. Infection, antibodies, and medications call all affect the circulating neutrophil pool. This is the pool of granulocytes sampled with a venipuncture. Interpretation of a peripheral WBC count can be difficult when trying to determine the risk of infection or underlying pathophysiology. A bone marrow examination can be very helpful in assessing granulocyte production and the risk of infection. Most WBC aberrations are secondary or reactive to a disease process, but occasionally rare hereditary disorders can present in the neonate. These are usually associated with an increased risk of infection (e.g., chronic granulomatous disease) or as part of a recognizable syndrome (e.g., Jobs syndrome). Congenital leukemia is extremely rare but striking leukemoid reactions can occur. Of note is the transient myeloproliferative condition or pseudoleukemia that may be observed in neonates with Down syndrome. Of prime importance when evaluating infants with any white cell aberration is the real risk of infection and the need for antimicrobials.

Platelet problems in the newborn present almost exclusively with thrombocytopenia and bleeding. Thrombocytopenia can be isolated or associated with other cytopenias. A low platelet count results from either decreased production or peripheral consumption of platelets. By examining the bone marrow and/or the mean platelet volume (MPV usually higher in younger platelets seen in consumptive disorders), the underlying pathophysiology can usually be identified. Most thrombocytopenias are consumptive and due to maternal antiplatelet antibodies, congenital infections, or part of complex DIC seen in sick newborns. It is paramount to compare the amount of clinical bleeding to the degree of thrombocytopenia in order to quickly make the right diagnosis and determine the need for transfusion or other therapy.

Hemorrhagic disease of the newborn is usually seen from day 2 to 4 of life resulting from vitamin K deficiency and the subsequent failure to produce clotting factors II, VII, IX and X. The prothrombin time is markedly prolonged and serious life threatening hemorrhaging can occur in many organ systems. This transient deficiency of vitamin K is thought to result from poor placental transfer, marginal content in breast milk, inadequate intake of breast milk and a sterile gut (lack of vitamin K producing GI flora). Hemorrhaging can be prevented by the intramuscular administration of prophylactic vitamin K shortly after birth.

Questions

1. True/False: Newborns with Down syndrome and elevated white counts and immature forms frequently progress to leukemia.

2. True/False: Factor VIII deficiency is on the vitamin K dependent factors leading to Hemorrhagic disease of the newborn.

3. Rh antibodies in mothers can result from:
    a. previous mismatched transfusions
    b. prior miscarriages
    c. fetal maternal transfusion
    d. all of the above.

4. True/False: Red cell problems are usually seen with abnormalities of white cells and platelets.

5. True/False: Neonatal immune thrombocytopenia can result from maternal auto sensitization or fetal maternal transfusion.

6. True/False: Thalassemia and hemoglobinopathies can present in the neonatal period with severe anemia.

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Answers to questions

1.F, 2.F, 3.d, 4.F, 5.T, 6.T

Chapter XI.6. Bleeding Disorders
Desiree Medeiros, MD

This 4 year old female is referred to the hematology department with a chief complaint of acute onset of easy bruising and "rash" for 3 days. She has not had epistaxis, oral bleeding, gross blood in urine or stools. She has never had palpable bruises, hemarthroses or deep muscle bleeds in the past. She has no history of fever or appetite changes. She had upper respiratory infection symptoms approximately 2 weeks ago. There is no travel history. She has 2 older brothers, neither of whom have had bleeding symptoms. Family history is negative for frequent nosebleeds, oral bleeding, menorrhagia or excessive bleeding with surgery or trauma. There is no history of malignancies, or autoimmune disorders.

Exam: VS are normal. Height and weight are at the 50th percentile. She is a healthy appearing, cooperative girl in no acute distress. HEENT exam demonstrates no signs of bleeding or bruising. Heart and lung exams are normal. Her abdomen demonstrates no hepatosplenomegaly. A diffuse petechial rash is noted on her neck, trunk, extremities and groin. Nonpalpable ecchymoses of varying ages are present on shins and arms. Her neurologic examination demonstrates no deficits.

CBC shows Hgb 12.8, Hct 38.5, WBC 6,000 with a normal differential. Platelet count is low at 5,000. PT and PTT 12.0 and 32 seconds, respectively. Review of the peripheral smear shows normal morphology of red and white blood cell lines. The platelets are reduced in number and the majority of them are increased in size. A bone marrow aspirate is not performed.

She is diagnosed with immune thrombocytopenic purpura. She is followed closely with weekly CBCs. Her bruises and petechiae fade by her next visit and her platelet count returns to 240,000 one month later.

Bleeding disorders can either be inherited or acquired and are due to defects in either primary or secondary hemostasis. While evaluating a child with a bleeding tendency, the history and physical examination should be directed at differentiating between these. An appropriate history can be more helpful in evaluating these children than any laboratory test. Bruising with or without preceding trauma can be due to a defect in either primary or secondary hemostasis although deep palpable bruises are usually due to a clotting factor defect. Petechiae are usually due to a platelet or blood vessel defect. One should ask about a history of mucosal bleeding (including epistaxis, oral bleeding, gastrointestinal, genitourinary and menstrual bleeding), bleeding from injury or following procedures such as circumcision and tonsillectomy, and deep tissue or musculoskeletal bleeding. Age of onset, frequency and severity of each bleeding complaint should be determined and an extensive family history and medication history should be obtained.

The child should be examined for signs of bleeding, such as petechiae, bruising, mucosal bleeding, and oozing from venipuncture sites. Differentiate between superficial bruises and deep palpable ecchymoses, making note of their location. Special attention should be made to the joints and large muscle areas, looking for deep tissue bleeding.

Laboratory studies assist in confirming suspicions raised from the history and physical. Routine screening laboratory studies should include complete blood count (CBC) with a platelet count, prothrombin time (PT) and activated partial thromboplastin time (PTT). Further specific testing should be performed based on the working diagnosis. These include a PTT mixing study (which helps differentiate a factor deficiency from an acquired inhibitor), bleeding time, factor assays, von Willebrand studies, and platelet aggregation tests. The bleeding time is an uncommonly ordered test during which a standardized small laceration is created on the patient's forearm and the time for the bleeding to stop is measured and compared to standard times. This test is prolonged in conditions of thrombocytopenia and platelet dysfunction. Platelet aggregation studies are special studies that can be done to test the aggregation of platelets in response to several known agents which induce platelet aggregation in vitro such as adenosine diphosphate (ADP), epinephrine and collagen.

The more commonly encountered bleeding disorders are discussed in further depth in this chapter.

I. Primary Hemostasis (platelets)
   A. Quantitative (thrombocytopenia)
      1. ITP
      2. Hemolytic uremic syndrome (HUS)
      3. Thrombotic thrombocytopenic purpura (TTP)
      4. Medications
      5. Marrow failure (leukemia, aplastic anemia)
      6. Platelet sequestration, consumption and dilution
   B. Qualitative (poor platelet function)
      1. Inherited platelet aggregation defect
      2. Drug effect
II. Secondary Hemostasis (coagulation)
   A. Congenital factor deficiency
      1. Hemophilia A and B
      2. von Willebrand disease
      3. Other factor deficiencies (rare)
   B. Acquired factor deficiency
      1. Vitamin K deficiency
      2. Liver failure
   C. Antiphospholipid antibody

Defects in Primary Hemostasis

Quantitative platelet disorders result in thrombocytopenia, either due to decreased bone marrow production or increased platelet destruction.

Immune Thrombocytopenic Purpura

Immune or idiopathic thrombocytopenic purpura (ITP) is one of the most common acquired bleeding disorders of childhood. Usually, it is a benign, self-limited disease that occurs in previously healthy children. The typical course in an untreated child is resolution of bleeding symptoms 3 to 10 days after diagnosis, regardless of the platelet count and an increase in the platelet count within 1 to 3 weeks. The platelet count returns to normal in 4 to 8 weeks in approximately half of patients and two thirds of children have resolution by 3 months after diagnosis. By 6 months, platelet counts have returned to normal (>150,000 per cubic mm) in 80% of patients. The remainder are defined as having chronic ITP (1,2). Most children follow a course consistent with acute ITP, in which the platelet counts are very low, but they recover as noted above. Adults more commonly follow a course consistent with chronic ITP, in which the platelet counts are usually moderately low, but the thrombocytopenia persists for long periods of time and often for life. If patients with chronic ITP sustain significant consequences from recurrent bleeding, a splenectomy is sometimes necessary to raise their platelet count.

ITP is an immune-mediated disorder in which circulating antiplatelet antibodies target epitopes on the platelet membrane (1). The antibody-coated platelets are subsequently destroyed by macrophages in the reticuloendothelial system. Children with ITP present with sudden onset of bruising, petechiae and occasionally epistaxis. There may be a history of a preceding viral infection or a recent live-virus immunization (1). There should be no evidence of other disorders causing thrombocytopenia, such as systemic lupus erythematosus or HIV infection. These children appear well except for bruises and petechiae. A minority of patients have mucous membrane hemorrhage, such as menorrhagia, gastrointestinal bleeding or oral blood blisters. They do not have jaundice, pallor, or hepatosplenomegaly.

The most important laboratory assessment in the evaluation of ITP is the CBC and peripheral blood smear. The platelet count is typically very low (<20,000 per cubic mm) and unless there is appreciable bleeding, the hemoglobin concentration is normal as is the leukocyte count. The peripheral smear shows normal morphology of all cell lines except the platelets are reduced in number and tend to be large. PT and PTT are normal and do not need to be performed. The bleeding time is predictably prolonged and unnecessary in the evaluation of a child with ITP. When indicated by the medical history and physical examination, evaluation for HIV, systemic lupus erythematosus, or Evan's syndrome should be considered. Bone marrow aspiration should be considered in patients with lymphadenopathy, hepatosplenomegaly, or other abnormalities on the CBC.

Management of ITP in a child includes education and reassurance of the child's parents. The child's activities should be limited, and aspirin and NSAID containing medications should not be used. Children without significant clinical bleeding may be closely observed with CBCs once or twice weekly. Once the platelet count begins to increase, it may be measured every 2 to 3 weeks until it returns to normal (>150,000). Once the platelet count has normalized, recurrence is rare and follow-up platelet counts are unnecessary (1,2). A few children with ITP have bleeding significant enough to warrant medical management. Standard therapy options include oral or IV corticosteroids (which block the reticuloendothelial system's destruction of antibody-coated platelets and reduce synthesis of antiplatelet antibodies), IVIG (IV gamma globulin which inhibits Fc receptors on phagocytes, allowing antibody-coated platelets to circulate and alters T-lymphocyte subsets and B-cell function and reduces autoantibody production), and Anti-D (which is the anti-serum against the Rh(D) antigen on erythrocytes and by coating Rh(D) positive erythrocytes, it decreases platelet destruction).

Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP)

HUS and TTP are closely related disorders caused by microvascular occlusion of arterioles and capillaries producing ischemia of multiple organs. HUS is a combination of thrombocytopenia, microangiopathic hemolytic anemia, and acute renal failure (4). It occurs mostly in children and has a fairly good prognosis. TTP is characterized by a pentad of features which include: thrombocytopenia, microangiopathic hemolytic anemia, neurologic disturbances, renal dysfunction and fever (4). It occurs in young adults and teenagers and carries a high mortality if unrecognized and not treated. Table 1 compares both disorders.

Table 1: Comparison of HUS and TTP

Feature	HUS	TTP
Course	Age usually <3 yr M=F Prodrome: infection, diarrhea Recurrence rare	Age usually 3rd decade F>M Prodrome less common Recurrence common
Diagnosis	Triad Acute renal failure Thrombocytopenia Microangiopathic anemia	Pentad CNS disturbance Thrombocytopenia Microangiopathic anemia Renal dysfunction Fever
Etiologic factors	E. coli, Shigella gastroenteritis, pneumococcus	Pregnancy, autoimmune disease, malignancy, drugs
Treatment	Renal dialysis Corticosteroids - no help Transfuse only if necessary	Plasma exchange Corticosteroids AVOID transfusions
Prognosis	Good	Poor

A variety of drugs have been reported to cause thrombocytopenia either by drug-induced platelet destruction or bone marrow suppression. Heparin merits special emphasis because it is so commonly used. Heparin does not inhibit platelet function but it may sometimes cause thrombocytopenia. There are two types of heparin-induced thrombocytopenia (HIT). The first occurs 2 to 5 days after initiation of heparin. Platelet counts rarely fall below 100,000 per cubic mm and normalize within 1 to 5 days. This type is thought to result from platelet aggregation secondary to a direct heparin effect (4). The second type of HIT occurs 3 to 15 days after the initiation of heparin (4). Platelet counts fall below 40,000. Arterial thrombosis may occur. The mechanism is immune mediated. Treatment involves discontinuation of heparin.

Decreased numbers of platelets result from impaired platelet production due to leukemia, aplastic anemia or bone marrow suppression due to viral infection or drugs. These are discussed in separate chapters. May-Hegglin anomaly is characterized by mild to moderate thrombocytopenia and the presence of Dohle bodies in the leukocytes. Kasabach-Merritt (giant hemangioma) syndrome is due to localized intravascular coagulation from low blood flow through the abnormal vascular tissue and is associated with thrombocytopenia (4). Foreign bodies in the circulation (central venous catheters and prosthetic valves) are sites for platelet consumption. Platelet loss also results from extracorporeal circulation and exchange transfusions. Massive plasma and blood transfusions lead to a dilutional thrombocytopenia. Finally, platelet counts may be low as a result of sequestration when the spleen is enlarged.

Qualitative platelet disorders (defects in platelet aggregation) are very rare. Most are inherited as autosomal recessive traits. Patients present with bleeding similar to that seen with thrombocytopenia. They complain of skin and mucous membrane bleeding, recurrent epistaxis, gastrointestinal bleeding, menorrhagia, and prolonged bleeding with injury or surgery (5). Aspirin (ASA) and non-steroidal anti-inflammatory drugs (NSAIDs) are common causes of temporary platelet dysfunction. Laboratory evaluation usually demonstrates a normal platelet count, prolonged bleeding time and abnormal platelet aggregation studies. Coagulation studies (PT, PTT) are usually normal. The most common platelet aggregation defects are described in table 2 below.

Table 2: Platelet aggregation defects

Condition	Platelet aggregation studies	Platelet count	Other
Glanzmann thrombasthenia	Abnormal to all agonists	Normal	
Bernard-Soulier syndrome	Abnormal to ristocetin	Decreased	Giant platelets
Storage pool defect (Dense body deficiency, Gray platelet syndrome)	Abnormal 2nd phase of aggregation	Normal	Abnormal platelet granules on electron microscopy
ASA/NSAID	Abnormal to arachidonic acid and abnormal secondary aggregation to ADP and epinephrine.	Normal	Drug induced enzyme effect inhibiting platelet granule release This is the most common cause of platelet dysfunction

Defects in Secondary Hemostasis

Hemophilia

Hemophilia is an X-linked inherited bleeding disorder transmitted from female carriers to their male children. It is due to a deficiency of factor VIII (Hemophilia A or "Classic hemophilia") or factor IX (Hemophilia B or "Christmas disease"). Hemophilia A is more common, occurring in 1/5000 male births while hemophilia B occurs in 1/15,000 (6). Signs and symptoms vary depending on the severity of the hemophilia. Severity is defined by baseline factor levels: severe <1%, moderate 1-5%, mild >5% (6,7). Children with severe hemophilia usually present in the first year of life with a history of extensive deep palpable ecchymoses. There may be a history of bleeding from the circumcision. After the age of 2 years, they begin to develop spontaneous hemarthroses or deep muscle bleeds. They can have mucosal bleeds, such as oral bleeding with procedures and hematuria. The bleeding is usually not catastrophic. Instead, it is prolonged and continuous without therapy. A head injury is considered an emergency since it is potentially life threatening if not treated appropriately. Children with milder forms of hemophilia may present later in life with a history of easy bruising or prolonged bleeding following injury. They usually do not have spontaneous bleeding. Laboratory findings include a markedly prolonged PTT (>100 seconds) and a decreased factor VIII or IX activity. Other screening tests (PT, platelet count and bleeding time) should be normal.

The mainstay of therapy is replacing the deficient clotting factor with factor VIII or IX concentrate (6,7). Both human derived and recombinant factor concentrates are available. In the past, factor replacement carried a risk of transmission of viral infections, especially hepatitis B and C, and HIV. This risk has been reduced with current viral inactivation techniques and with the availability of recombinant factor. Each unit of factor VIII will increase the factor VIII level by 2% and has an 8 to 12 hour half-life. Each unit of factor IX will increase the factor IX level by 1% and has an 18 to 24 hour half-life (6,7). Dosing depends on the location and severity of the bleed. In addition to factor replacement, males with hemophilia benefit from supportive measures, physical therapy and often require orthopedic intervention. Aminocaproic acid is an oral antifibrinolytic and can be used adjunctively to treat mucous membrane bleeding. Mild factor VIII deficient patients may be treated with intravenous or highly concentrated intranasal desmopressin (DDAVP) which causes a release in endogenous factor VIII stores. These boys need to be cautioned to avoid contact sports such as tackle football, boxing or wrestling. It is nationally recognized that hemophilia treatment centers have improved the prognosis of patients with hemophilia. Patients and their families have a home supply of factor and infuse themselves promptly at the earliest sign of a bleed. Prophylaxis has been instituted in most severely affected individuals where they infuse themselves regularly two to three times a week and/or prior to a sports activity in order to prevent spontaneous bleeds. This has reduced much of the chronic arthropathy in this population. Today, young people with hemophilia can lead independent and nearly normal lives.

von Willebrand Disease

von Willebrand disease (vWD) is the most common inherited bleeding disorder. It affects 1% to 2% of the population. von Willebrand factor is a cofactor for platelet adhesion and a carrier protein for factor VIII (8,9). The most common form is transmitted as an autosomal dominant trait. Severity of bleeding symptoms depends on the type and subtype. Types 1 and 3 result in quantitative defects of the von Willebrand protein (i.e., deficiency) while Type 2 is due to a qualitative defect in the von Willebrand protein. The vWD types are listed in table 3.

Table 3 - von Willebrand disease subtypes

Type	Defect	Bleeding symptoms
Type 1 (common)	Quantitative: Decreased vWF	Mild
Type 2 (uncommon)	Qualitative: Normal vWF levels	
2A	vWF not "sticky" enough	Variable
2B	vWF too "sticky"	Potentially severe
2N	Lacking receptor for factor VIII binding	Similar to hemophilia
2M	Lacking receptor for platelet binding	Fairly mild
Type 3 (rare)	Quantitative absent vWF	Severe

Patients with vWD often have a positive family history of bleeding and easy bruisability in addition to the personal bleeding history. The bleeding symptoms can be similar to that seen with thrombocytopenia or platelet dysfunction and usually involve the mucous membranes and patients present with complaints of recurrent epistaxis, oral bleeding with dental care, and menorrhagia. In addition, they often have a history of easy or spontaneous bruising and post-operative bleeding. More rarely, one may elicit a history of gastrointestinal or genitourinary bleeding. Types 2N and 3 may also have deep tissue bleeding, similar to the bleeding seen in moderate or severe hemophiliacs.

The most useful screening tests in patients with suspected vWD are bleeding time, PTT and von Willebrand factor activity (ristocetin cofactor). Ristocetin cofactor is a functional assay of the von Willebrand protein. At least one of these screening tests will be abnormal in 97% of patients with vWD (10). Other useful studies include platelet count, von Willebrand factor (vWF) antigen and factor VIII activity. Once the diagnosis of vWD is made, the vWF multimeric assay and platelet aggregation studies will determine the type of vWD. With deficient or defective von Willebrand factor, there will be abnormal platelet aggregation to ristocetin. Other platelet aggregation studies should be normal.

It is important to keep in mind that vWF is an acute phase reactant and therefore, studies for vWD can be affected by cigarette smoking, stress, exercise, pregnancy, corticosteroids, birth control pills, etc. In addition, people who are blood group O have a lower normal range for vWF antigen and ristocetin cofactor activity. When there is a strong suspicion that a patient has vWD, the laboratory evaluation may need to be repeated up to 3 times.

In most cases of vWD the bleeding symptoms are quite mild, and therapy includes education and measures for local control of bleeding. Aminocaproic acid is useful in treating mucous membrane bleeding. Desmopressin (DDAVP) causes a release of factor VIII and vWF from storage sites and is useful in treating bleeding symptoms in patients with mild (type 1) vWD. Patient with severe forms of vWD (type 3) or a qualitative defect of the vWF (types 2A, 2B, 2N) may need replacement with Humate-P (a factor VIII product

containing vWF) (8,9). Once diagnosed and followed and treated in a comprehensive hemophilia treatment center, people with vWD can lead normal lives.

Other Factor Deficiencies

Deficiencies in other fluid factors are much more rare than deficiencies in factors VIII, IX or vWF. Factor XI deficiency presents with variable bleeding and a prolonged PTT. Bleeding symptoms do not correlate with the factor level (11). It is more common in the Ashkenazi Jewish population. Deficiencies of the contact factors (factor XII-Hageman factor, high molecular weight kininogen, and prekallikrein) are associated with a significantly prolonged PTT without bleeding symptoms (11). Deficiencies of factors II, V, VII, X and XIII are very rare. For most of these, bleeding symptoms occur in those whose factor levels are <5% to 10% (11). Factor VII deficiency should be considered with isolated prolongation of the PT. Factors II, V, and X are common pathway factors and present with prolongation of both PT and PTT. Factor XIII deficiency is associated with bleeding from the umbilical stump and intracranial hemorrhage with a normal PT and PTT. It is only symptomatic in patients whose level is <1%. Treatment consists of replacement of the deficient factor with fresh frozen plasma or, if available, specific factor concentrate (11).

Acquired Defects of Secondary Hemostasis

Vitamin K is needed for the synthesis of factors II, VII, IX and X. Vitamin K is vital to the carboxylation of glutamic acid residues which is needed for the calcium and phospholipid-dependent activation of these factors (1). The most common circumstance in which vitamin K deficiency leads to bleeding is hemorrhagic disease of the newborn. Without vitamin K supplementation, significant GI and cutaneous hemorrhage may develop within a few days (1). After the newborn period, vitamin K is absorbed from the GI tract. Deficiency may then result from nutritional deficits, malabsorption, or alteration in intestinal flora. Treatment must be directed at the underlying disorder and vitamin K supplementation.

Decreased synthesis of coagulation proteins occurs in severe liver disease. Abnormalities in the liver's capacity to synthesize one or more clotting factors may result in problems with hemostasis. Treatment involves replacement of the decreased factor(s) with fresh frozen plasma. Liver disease may also lead to portal hypertension and platelet sequestration in the spleen.

Disseminated intravascular coagulation (DIC) occurs in patients who are critically ill and therefore, rapid diagnosis is essential. Fever, hypotension, acidosis, oliguria, or hypoxia may be present. In addition, petechiae, purpura, and oozing from wounds and venipuncture sites may develop. Although not always clinically evident, microvascular and large vessel thrombosis may occur. The platelet count is typically decreased due to consumption and platelet destruction. The PT and PTT are prolonged from depletion of factors V, VIII, IX, and XI. Fibrinogen is decreased. Fibrin degradation products and the D-dimer assay are increased. The mainstay of therapy is to treat the underlying disease. However, this may not always be enough to correct serious bleeding or thrombosis. Additional therapy consists of replacing clotting factors and platelets and possibly the use of heparin and antifibrinolytic agents (1).

Circulating inhibitors such as heparin and the lupus anticoagulant (antiphospholipid antibody) often lead to abnormalities in screening coagulation laboratory values. These cause a prolonged PTT which is not corrected with 1:1 dilution with normal plasma (the PTT mixing study). If the patient has a factor deficiency such as hemophilia, adding normal plasma to the patient's plasma, will partially correct the factor deficiency and the PTT will normalize. If the PTT does not normalize by adding normal plasma, this implies that an anticoagulant is present in the patient's plasma. The term “lupus anticoagulant” is misleading because it can occur in many clinical settings other than in SLE and the anticoagulant effects are only observed in vitro with prolongation of the PTT, but not with excessive bleeding. Instead, when it occurs in adults, it may be associated with spontaneous abortion, and thromboembolism. In the pediatric population, it usually occurs in otherwise healthy children, often following a viral illness and is transient with rare clinical sequelae (1).

A summary of laboratory studies for bleeding disorders is listed below. Routine tests are commonly ordered by non-hematologists. Special tests are not ordered routinely and are only ordered (most commonly by hematologists and other subspecialists) when a bleeding disorder is highly suspected.

	Tests for:	Abnormal in:
Routine tests:		
Platelet count	Disorders of platelet quantity	ITP, HUS, TTP, thrombocytopenia due to bone marrow suppression, platelet consumption.
PT	Extrinsic and common coagulation Pathway (factors I, II, V, VII, X)	Factor deficiency (I, II, V, VII, X), liver failure, vitamin K deficiency, coumadin, warfarins.
PTT	Intrinsic and common pathway (factors I, II, V, X, VIII, IX, XI, XII)	Factor deficiency (I, II, V, X, VIII, IX, XI, XII), heparinization, circulating anticoagulants, vWD
Special tests:		
PTT mixing study	Circulating anticoagulants.	PTT corrects with factor deficiency, but it does not normalize with circulating antibodies/anticoagulants.
Bleeding time	Platelet function	ASA, NSAIDs, platelet function disorders (see table 2), vWD
Platelet aggregation	Platelet function	ASA, NSAIDs, platelet function disorders (see table 2), vWD
Ristocetin cofactor	vWF function	vWD
vWF antigen	vWF quantity	vWD
vWF multimeric assay	Defines type of vWD	vWD

Questions

1. What is the mechanism for the thrombocytopenia in ITP?
2. What is the classic triad associated with hemolytic uremic syndrome?
3. How is hemophilia inherited?
4. Describe some indications for factor VIII administration in a patient with hemophilia A.
5. What are the functions of von Willebrand factor?
6. What combination of laboratory tests are good screening studies for von Willebrand disease?
7. Why is it important to test for blood type in a person with suspected von Willebrand disease?
8. Name the vitamin K dependent factors.
9. Explain why the addition of normal plasma to a patient's PTT test, will help to identify a circulating anticoagulant such as the lupus anticoagulant.

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Answers to questions

1. ITP is an immune-mediated disorder in which circulating antiplatelet antibodies target epitopes on the platelet membrane. The antibody-coated platelets are subsequently destroyed by macrophages in the reticuloendothelial system.
2. Thrombocytopenia, microangiopathic hemolytic anemia, and uremia.
3. X-linked recessive.
4. Following trauma or injury, especially head injury; to treat spontaneous bleeding, such as hemarthrosis or deep muscle bleeding, and prior to procedures, including dental work.
5. von Willebrand factor is a cofactor for platelet adhesion and carrier protein for factor VIII.
6. Bleeding time, PTT, and ristocetin cofactor.
7. Patients who have blood group O have a lower normal range for von Willebrand studies.
8. Factors II, VII, IX, and X.
9. If the prolonged PTT is due to a factor deficiency, then the addition of factors from the "normal plasma", will correct the PTT. However, if the PTT is due to a circulating anticoagulant such as heparin or a lupus anticoagulant, the circulating antibody will inhibit the "normal" factors and the PTT will remain prolonged. Failure to normalize the PTT after the addition of normal plasma, implies the presence of a circulating anticoagulant.

Chapter XI.7. Transfusion Medicine
Kelley A. Woodruff, MD

A 7 year old boy is being worked up for profound pancytopenia. He was well until one week ago when his grandparents noted pallor. He has had no recent history of fever, and is otherwise well. He was initially seen yesterday in the hematology clinic, where a CBC showed a hemoglobin of 5.3 g/dl, WBC 1.9 K/ml with 96% lymphocytes, and a platelet count of 4,000. He has a bone marrow aspirate scheduled for tomorrow. He is brought back in to the clinic today, because he has epistaxis, which has been ongoing for 1 hour now. He states he feels weak and dizzy.

Exam: He is afebrile, BP 110/40, HR is 186 with a mild gallop. Weight is 26 kg (75%ile). He is lying down, with a tissue to his nose, and bright red blood is dripping out. He is alert and oriented, nontoxic, and comfortable. He is pale appearing, conversing appropriately, and no other overt bleeding is noted. His abdomen is benign.

CBC today shows hemoglobin 5.1, WBC 1.3, and platelet count 5,000. After IV access is obtained, he is given a fluid bolus and a "type and hold" for blood status is ordered.

The start of transfusion medicine occurred during World War II when the major blood types A, B, AB and O, and Rh factor were identified. Type A persons have A antigen on the membrane of their red blood cells. They develop anti-B antibodies shortly after birth without any prior antigenic stimulation, thus these antibodies are called natural antibodies. Type B persons have B antigen on the membranes of their red blood cells, and such persons naturally have anti-A antibodies in their plasma. Type AB persons have both A and B antigens, and no anti-A or anti-B antibodies in their plasma. Type O persons, who lack these major red cell membrane antigens, have both anti-A and anti-B antibodies. When crossmatching a unit of blood for a transfusion, the biggest concern is to avoid giving the patient antigen that would react with their own antibodies. Thus, people with type O blood are considered to be universal donors, with regard to red blood transfusions, since there are no major (A or B) antigens on their red blood cells.

Most transfusions of red blood are given as packed red blood cells (PRBCs) that have most of the plasma removed. Each unit of PRBCs is about 250 ml, depending on the type of preservative used, and each ml provides 1 milligram of elemental iron. The fastest rate of transfusing a patient should be 5 ml/kg/hour. Generally, a transfusion is ordered as 10-15 ml/kg given over 2 to 3 hours.

The advent of platelet transfusions in the early 1970's changed the survival rate for many diseases. Today, single donor platelets are usually considered the optimal product for most platelet transfusion needs. A single donor unit of platelets is based on the adult dose and contains about 225 ml per unit. It is obtained via pheresis from one donor and takes about 4 hours to donate, compared to 30 minutes to donate one pint of whole blood. Platelets extracted from a unit of whole blood (called random platelets) contain about 50 ml per unit. Usually about 6-8 random units (i.e., 6-8 different donor exposures!) need to be pooled together to equal the volume of one unit of single donor platelets. Single donor platelet transfusions are usually given over 1 hour.

A hemolytic transfusion reaction results when an antibody-antigen reaction causes (donor) red cell lysis. It is most severe when a patient has circulating antibody that reacts with donor antigen (RBCs). Some antigens produce stronger hemolytic reactions than others. For example, transfusion reactions involving A and B antigens will cause a brisk, severe hemolysis, leading to fatalities from renal failure. The Duffy and Kell antigens also cause significant hemolysis. The Lewy antigen leads to a mild hemolysis that is not usually fatal (remembered by the mnemonic Duffy dies, Kell kills, and Lewy lives). There are many other less common antigens, natural and acquired, that are screened for in the direct antibody test (DAT) during crossmatching. A patient having a hemolytic transfusion reaction may present with lower back pain, and hemoglobinuria. The treatment consists of supportive care, especially intravenous hydration to help protect the kidneys from damage. Corticosteroids may also be beneficial.

Another type of transfusion reaction is associated with urticaria, or less commonly, fevers. These reactions are typically caused by extraneous donor proteins, which are foreign to the recipient. These proteins are usually carried in the plasma of the donor product. Therefore, such reactions are usually seen more often with platelet transfusions than with red cell transfusions, since the platelet products carry more plasma than the packed red cell units. Urticaria reactions are usually mild, and treated with diphenhydramine and sometimes IV corticosteroids. Epinephrine is only rarely required. Fevers are usually mild and self-limited, and can be managed with acetaminophen.

Irradiation of blood products will inhibit the replication of nucleated cells (e.g., WBCs) in the donor product, by damaging their DNA. This radiation dose will not kill common organisms known to contaminate blood products. All transfusion products have donor stray white blood cells, which, in theory, could replicate when transfused into an immunocompromised host. This would cause a graft versus host (GVH) situation, which, when arising from a blood transfusion, is often fatal. Therefore, all blood products given to infants, oncology patients, or other immunocompromised hosts should be irradiated. The exception, of course, is a stem cell product for a stem cell (bone marrow) transplant. If these stem cells were irradiated, the new graft would not grow, and there would be no transplant.

Infusion filters should be used for all transfusions of packed red blood cells and platelets. The only exception to this is the infusion of a stem cell product for any type of stem cell transplant. There are many types of filters. Their main purpose is to filter out either extraneous white blood cells or large foreign proteins. The use of a filter during a transplant of stem cells would filter out the very stem cells that are intended for the patient! Since filters will not dependably remove all white blood cells, filters cannot replace irradiation to prevent graft versus host disease.

Infections acquired from transfusions are rare due to improved screening methods by blood banks. Infectious agents that can be transmitted through transfusions include HIV, Hepatitis B, Hepatitis C, Parvovirus and malaria. Blood is actively screened for all these agents and discarded if contamination is even suspected. Cytomegalovirus (CMV) infection can also be transmitted through blood transfusions. It is harbored in a dormant state in the white blood cells of previously infected persons. Since 80% of most adult populations are positive for past CMV infection, most donated blood is CMV serology positive. CMV infection can be transmitted to severely immunocompromised persons with no prior infection. Such an incident might occur during a bone marrow transplant. Since newborns up to age 4 months are considered immunocompromised and have no previous CMV infection, all newborns receive CMV negative blood.

Clinicians should familiarize themselves with the options for ordering, holding, or preparing for a PRBC transfusion. A "draw and tag" should be ordered for a patient who might possibly need a transfusion during the hospital stay (but the probability of this is low). In this case, a blood sample is drawn from the patient and the patient is tagged with a special blood products identification bracelet which is matched to the specimen drawn and a set of labels which will be used on any blood products which might be ordered for the patient in the next few days. If blood products are required for this patient, they can be ordered from the blood bank. The blood bank will crossmatch the blood using the previously drawn and labeled specimen.

A "type and hold", also called a "type and screen", should be ordered for a patient who has a moderate likelihood of requiring a transfusion during the hospital stay. The patient is drawn and tagged as in the "draw and tag" procedure. Additionally, the patient's blood type and Rh are determined and a screening test is performed for unexpected antibodies and minor compatibility group profiling. Thus, the patient's blood type and Rh are known which saves some time in case a crossmatch is needed.

A "type and crossmatch" should be ordered when the patient will be getting a transfusion. The patient is drawn and tagged. The patient's blood type, Rh, and antibody screens are performed. A unit of blood is then selected for the patient and compatibility testing is performed with the patient's specimen and the donor unit's PRBCs. This unit is then held for the patient. This unit cannot be used for any other patient, so a "type and crossmatch" should only be ordered when a transfusion is highly likely.

In a true emergency with a rapidly hemorrhaging and hypovolemic patient, the time required for blood typing and crossmatching (20 to 30 minutes) may not be available. Transfusing with O negative PRBCs (if available) is the best emergency option. In the meantime, a type and crossmatch should be in progress. Type specific blood (the patient's type and Rh are known, but a crossmatch has not yet been performed) is sometimes useful until a crossmatch is completed.

There are many ethical issues which need to be considered when transfusing patients. Because of the rare possibility of morbidity and mortality from transfusions, written and informed consent must always be obtained before a transfusion is given. The patient (or patient's guardian) must be fully informed of the rare possibilities of infectious agents and transfusion reactions. Full consideration must be given to the necessity of a transfusion. In short, if spontaneous resolution of the problem (anemia, thrombocytopenia, or other morbidity in which a transfusion is thought to be beneficial) can be expected, or if alternative treatments exist, the transfusion should be avoided. When considering a transfusion, the actual morbidity and mortality from the underlying problem itself, without a transfusion, must be weighed against the rare problems that may result from the transfusion itself. Adult patients may refuse a transfusion for themselves, regardless of their reasons, even in the face of death (e.g., Jehovah's Witness patients). A parent may also refuse a transfusion for their child. However, if a physician strongly believes that a child has a life-threatening condition that can only be effectively treated with a transfusion of a blood product, the physician is obligated to take legal action.

Questions

1. In the case above, you decide to transfuse the 26 kg patient with both PRBCs and one unit of single donor platelets. Which is the best way to transfuse the PRBCs?
   a. Transfuse 2 units, each over 6 hours, with furosemide in between the units.
   b. Transfuse 1 unit over 3 hours
   c. Transfuse 390 ml over 4 hours
   d. Transfuse 260 ml over 2 hours

2. During the transfusion of platelets, this patient develops 3 small hives (urticarial lesions) on his back. Which is the correct response? No pre-medications were given.
   a. Continue the transfusion. Stop and medicate if more hives appears.
   b. Stop the transfusion. Give diphenhydramine and proceed when the hives clear.
   c. Stop the transfusion. Draw blood for type and cross to check the crossmatch for that unit. Give diphenhydramine, and proceed with the same unit when the hives clear, and if the repeated crossmatch is OK.
   d. Stop the transfusion. Give diphenhydramine and methylprednisolone, and proceed when the hives resolve.

3. During the transfusion of PRBC, the child starts to complain of lower back pain during the transfusion. What is most likely happening?
   a. A febrile reaction from donor white blood cells causing an inflammatory response.
   b. A hemolytic reaction involving donor antibodies to recipient red blood cells.
   c. A hemolytic reaction involving donor red blood cells and recipient antibodies.
   d. Recipient mast cell histamine release, stimulated by donor antigen presenting cells.

4. All of the following should be done with this complaint of lower back pain, EXCEPT:
   a. Consider IV corticosteroids.
   b. Hydrate with IV fluid bolus.
   c. Repeat crossmatch with unit of blood being transfused.
   d. Administer subcutaneous epinephrine.

5. Which of the following children should receive a transfusion of PRBC?
   a. A 2 year old with Hgb 2.8 g/dl (etiology unclear at the moment), HR 200, with gallop.
   b. A 2 year old Jehovah's Witness with Hgb 2.8 g/dl (etiology unclear at the moment), HR 200 with gallop.
   c. A 4 year old just diagnosed with Neuroblastoma, Hgb 6.8 g/dl, HR 134.
   d. A 13 year old girl, presents with butterfly rash on her face, has fevers, Hgb 6.8 g/dl, rales, splenomegaly, HR 156.
   e. All of the above

6. Irradiation of blood products:
   a. Will prevent donor white blood cells from proliferating in the recipient's body.
   b. Will kill many common infections that could be transmitted in extraneous donor WBC or plasma.
   c. Could, in theory, take the place of blood filters.
   d. Is very expensive and tedious, and therefore should be used in only selected cases.

7. An 11 month old boy weighs 7.5 kg, and has Fe deficiency anemia with a Hgb 2.2 g/dl. HR is 188. You decide to transfuse him. Which is the best way to transfuse him with PRBCs (checking the Hgb at appropriate intervals)?

a. Transfuse 150 ml over 12 hours.
b. Transfuse 2 half units, each over 4 hours.
c. Transfuse 15 cc/kg, i.e. about 112 ml slowly over 6 hours, then start oral Fe.
d. Transfuse slowly at <3ml/kg/hour, with subunits from a unit split in the blood bank, and discard the remainder of each subunit after 4 hours.

8. All are true of a neonatal unit (of red blood cells) EXCEPT:

a. Always CMV negative.
b. Always irradiated.
c. Intended only for babies <2 months of age.
d. Always O negative.

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Answers to questions

1. b. Once a unit is spiked (IV infusion begun from unit bag), any uninfused blood must be discarded after 4 hours. Thus, the most time allowed for 1 unit to run is over 4 hours. Therefore, a unit may not be transfused over 6 hours. Giving 390 ml would give this patient 15 ml/kg, but giving this over 4 hours would be slightly too fast with such a low and fast falling hemoglobin. Additionally, it would expose the patient to a second donor, and half of the second unit would be discarded (wasted). Giving 262 ml means giving 1 unit (about 250 ml), and about 10 ml from a second unit (discarding the rest). Giving this over 2 hours would also be too fast as noted.

2. b. For just a few hives, it is not necessary to check the crossmatch of the blood, since this will detect antibodies causing hemolysis. Urticaria is not a hemolytic reaction. Usually diphenhydramine alone can resolve the hives, and the same unit can be continued with the diphenhydramine in effect.

3. c. See text

4. d. Epinephrine has no known beneficial effect on the hemolytic process.

5 e. All of these children should probably receive a transfusion.

6. a. See text

7. d. A unit of PRBCs can be split in the blood bank (like neonatal units) so that only one part of this is out of the blood bank and infusing into the patient at a given time (which can infuse up to 4 hours). Additionally, a child with such an extremely low hemoglobin needs to be transfused very slowly, at least initially, so as not to push his already compromised heart into further failure. With severe anemia, the patient is already in high output congestive heart failure. Blood is a potent volume expander which can suddenly worsen the CHF. Thus, the transfusion must proceed very slowly under close hemodynamic monitoring.

Chapter XI.8. Neutrophil Disorders
Wade T. Kyono, MD

Case 1

This is a 13 month old female who is referred to you for cold symptoms, fever (T 38.5 degrees) and a persistently low absolute neutrophil count (ANC = WBC x (segs% + bands%)) of 40 (WBC 4.0, 1% bands, 0% segs). Her ESR is 12. She was hospitalized three weeks ago for a pseudomonas external otitis media and neutropenia that was treated with two weeks of intravenous antibiotics. Three weeks ago, her ANC was 342, with a low of 54, and at discharge her ANC was 896 (one week ago). She had been doing well since discharge until her current illness.

Of note, a CBC at birth and at 10 months of age demonstrated normal absolute neutrophil counts. There is no history of increased bacterial or fungal infections. There is no family history of recurrent bacterial infection, neutropenia, immunodeficiency disease, autoimmune disease, or malignancy. There is no history of infant deaths in the family. There has been no history of recent medication use.

Exam: VS are normal. Height and weight are at the 75th percentile for age. Physical examination had no unusual findings. No oral thrush, lymphadenopathy, hepatosplenomegaly, or skin lesions are noted.

She is hospitalized for IV antibiotics (ceftazidime). Blood cultures return negative and she is discharged after 3 days. During this hospital stay she does well. Antineutrophil antibody testing is sent off to a specialized reference laboratory and it returns positive. A bone marrow examination is done (mostly because of parental concern) which shows a normal cellular marrow. During subsequent febrile illnesses, she does well clinically. Three months later, after she initially presented with neutropenia, her ANC improves to 2400. Two months later, it remains over 2000.

Diagnosis: Chronic benign neutropenia of infancy and childhood.

Case 2

This is a 2 year old male who presents with a chief complaint of recurrent skin and soft tissue infections. The infecting organisms were catalase producing bacteria. Three nitroblue tetrazolium (NBT) slide tests sent to a reference laboratory returned normal. Screening tests of humoral, cell mediated, and complement mediated immunity were normal. Referral is now being made to a hematologist during his current hospitalization for the treatment of cervical lymphadenitis and left lower lobe pneumonia with bilateral pleural effusions. The patient's blood samples were sent to a neutrophil research laboratory with results that demonstrated no reduction of NBT (an abnormal result in contradiction to the normal NBT slide test results) and negligible quantitative production of superoxide. His mother demonstrated an intermediate production of superoxide and a decreased number of neutrophils capable of reducing NBT.

Past Medical History: At 2 months of age, he developed a perianal furuncle that was incised and drained because of no response to oral antibiotics. At 5 months of age, he had surgical treatment for multiple perianal fistulas with abscesses. At 7 months of age, he had a left inguinal Klebsiella pneumoniae lymphadenitis that was treated with incision and drainage and oral amoxicillin/clavulanic acid. Two weeks later, a left subauricular lymph node abscess was incised and drained and a persistent perianal fistula received topical treatment with silver nitrate. Pseudomonas aeruginosa grew out of cultures of the neck abscess and the patient was hospitalized for intravenous antibiotic treatment and immunological evaluation. In addition to his subauricular lymphadenitis, he had a left calf cellulitis that grew Serratia marcescens and a left inguinal abscess that grew Staphylococcus epidermidis.

Clinical Course: He completes treatment with 6 weeks of intravenous antibiotics until his ESR decreases <30. However subsequently, he develops a slight limp at which time a large lytic bone lesion is found in the distal left tibia on plain x-rays. Culture of that lesion grows out Staphylococcus aureus after debridement and curettage. He receives 6 more weeks of intravenous antibiotics until his ESR is in the normal range. He is placed on subcutaneous injections of gamma interferon (three times a week) and twice daily doses of oral trimethoprim-sulfamethoxazole and has not required any further hospitalizations for bacterial infections for the last 3 years.

Diagnosis: Chronic granulomatous disease.

Neutrophils (polymorphonuclear leukocytes) represent the first line of active defense against bacterial and fungal invasion for the innate immune system. Though a critical component of the body's immune system, primary disorders of neutrophil function account for only about 18% of all primary immunodeficiencies, with T cell (20-30%) and B cell deficiencies (50%) comprising the majority of defects seen. Despite the relative rarity of primary neutrophil defects, clinical situations in which neutrophil function is decreased, such as prematurity, are commonly associated with increased rates of invasive bacterial infection. Primary deficiencies of neutrophil numbers or function are usually associated with an increased risk of serious, often life-threatening infections. Secondary deficiencies of neutrophil numbers or function are usually markers of systemic disease and tend to be clinically benign.

The most common problem seen by primary care physicians is neutropenia (decreased neutrophil count). Acute inflammatory processes are commonly associated with normal or reactive increases in neutrophil counts. When low neutrophil counts are associated with infection it must be decided whether neutropenia is secondary to the infection, or if an underlying neutropenia contributed to the risk of infection. A key point to remember is that the risk of infection with neutropenia is high when bone marrow production of neutrophils is decreased from either primary or secondary causes.

In general, common disorders are usually benign clinically and occur in children with no significant medical history of bacterial or fungal infections. Rare congenital disorders result in extremely high risks of infection and require specialized laboratory tests to correctly diagnose.

The most common presentation of neutropenia (low neutrophil counts) and neutrophilia (high neutrophil counts) is an acute febrile illness in an otherwise normal child. Serious primary neutropenia or primary disorders of neutrophil function are associated with "frequent" or "atypical" bacterial infections. These important points should be kept in mind: i) An overwhelming, sudden onset of sepsis, as observed in children receiving intensive multi-agent chemotherapy, is rare in most children with neutropenia or defects in neutrophil function. ii) An intact humoral and T-cell immune response and monocytosis compensates somewhat for a decreased neutrophil count or altered neutrophil function. iii) Little or no increased propensity to infection is associated with the most common form of severe neutropenia in children, so-called "chronic benign neutropenia". iv) Neutrophil defects commonly present with frequent, indolent bacterial or fungal infections that are difficult to detect and treat.

While there are subtle differences in the presentation of primary neutrophil disorders, the overlap in presentation is significant and determining the precise defect is impossible on clinical findings alone. With the passage of time it is generally easy to determine that a child's history of infections is abnormal, suggesting a more serious disorder.

DISORDERS OF NEUTROPHIL NUMBERS

Key to the understanding of quantitative abnormalities of neutrophil counts is an understanding of neutrophil distribution. The peripheral neutrophil count reflects the equilibrium between the circulating pool and the marginated pool of neutrophils adherent to vascular endothelium, and a tissue pool. The complete blood count (CBC) only monitors neutrophils in the circulating pool.

NEUTROPHILIA (increased neutrophils): Upon infection and activation of the immune response, neutrophils from the marrow storage pool are released resulting in up to three fold increases in neutrophil counts within four to five hours. More than half of the peripheral granulocytes are attached to the vascular endothelium at any given time point and represent a "marginated" pool that can be released almost immediately at times of stress. Epinephrine mediated "demargination" of neutrophils to the circulating pool is sometimes seen during phlebotomy in an anxious child and can result in spuriously elevated mature neutrophil counts. Among the other causes of neutrophilia are: reactive leukocytosis, ethnic neutrophilia, Pelger Huet, leukemoid reaction, leukoerthyroblastic response, chronic myeloid leukemia and leukocyte adhesion defect.

NEUTROPENIA (decreased neutrophils): Neutropenia is defined by an absolute neutrophil count (ANC) <1,500/cubic mm. ANC = (%bands + %mature neutrophils) X total WBC count. Decreased neutrophil production, storage, or release; redistribution from circulating to marginated pools; or increased destruction explains most cases of neutropenia. The key determinants of infection risk are the adequacy of the bone marrow storage or reserve pool and the general robustness of the immune response. These determinants affect the ability to deliver neutrophils to infected sites and the ability of the immune system to compensate for quantitative deficiencies in neutrophils. Neutropenia discovered during the evaluation of infection is generally a secondary finding and characterizes the general low risk of infection associated with a normal marrow reserve and immune system. Some of the causes of neutropenia are summarized below:

1. Kostman syndrome: primary decrease in bone marrow reserve; AR (autosomal recessive), AD (autosomal dominant), S (sex linked recessive); extremely rare; severe neutropenia in the newborn.
2. Shwachman-Diamond Syndrome: primary decrease in bone marrow reserve; AR, S; extremely rare; steatorrhea from exocrine pancreatic deficiency; metaphyseal dysplasia; 50% survival; 1/3 progress to myelodysplastic syndrome or acute myeloid leukemia; normal sweat chloride.
3. Cyclic neutropenia: primary cyclic (every 21 days) variations in bone marrow reserve; AD, S; 1-2 per million; regularly recurring fever every 21 days with oropharyngeal and skin infections; diagnose with CBCs 2-3 times per week for 8 weeks.
4. Chemotherapy: direct toxicity to neutrophil precursors results in a severe reduction in bone marrow reserve (severity dependent on the intensity of chemotherapy agents used); generally a high risk of infection with poor marrow reserve and generalized suppression of the immune system.
5. Nutritional: protein-calorie malnutrition, B12 deficiency, copper deficiency can result in ineffective myelopoiesis; treat by correcting deficiency.
6. Viral infection: bone marrow suppression from a direct effect of infecting virus or through an immune mechanism.
7. Chronic benign neutropenia of infancy and childhood: normal bone marrow reserve; generally thought to be mediated through an anti-neutrophil antibody; common; median age of detection 8 months, 90% detected before 14 months; most resolve spontaneously within months of diagnosis; no significant propensity to infection; treatment is supportive.
8. Autoimmune neutropenia: generally with normal bone marrow reserve but may be associated with a late maturational arrest; antibody mediated destruction of neutrophils; may have an associated primary autoimmune disorder.
9. Alloimmune neutropenia: normal bone marrow reserve; secondary to maternal anti-neutrophil antibody that has crossed the placenta; resolves by 3-4 months of age; generally supportive care.
10. Drug-induced neutropenia: normal bone marrow reserve but has been associated with a late maturational arrest; antibody or complement mediated neutrophil destruction; treatment consists of stopping unnecessary medications.
11. Infection related neutropenia: normal bone marrow reserve; virus induced anti-neutrophil antibody; parvovirus B19 and HIV can be screened; no treatment generally necessary.
12. Hypersplenism: normal bone marrow reserve; sequestration/possible destruction of neutrophils in the spleen; associated with malaria, TB, neoplasm, collagen-vascular diseases, hemolytic anemia; spherocytes and tailed RBC on blood smear; treat underlying disorder.
13. Pseudo-neutropenia (severe infection): normal bone marrow reserve; generally associated with increases in marginated and tissue pools; mild and spontaneously resolves.

In general, the risk of infection can be related to the bone marrow reserve and overall immune competence of patients with neutropenia. Careful consideration of the overall risk of infection needs to be utilized to determine the appropriate management of these children. Inadequate treatment or follow-up of children with neutropenia and a high risk of infection can be fatal, while over aggressive treatment of a child with a benign neutropenia may result in inappropriate medical care and unnecessary morbidity.

These guidelines can be used in the evaluation and management of the child with neutropenia:

1. Patients with ANCs <500 and fever require prompt evaluation and the rapid initiation of broad spectrum parenteral antibiotics.
2. Empiric parenteral antibiotic therapy (consider ceftazidime, vancomycin, or meropenem) to cover S. aureus, Pseudomonas aeruginosa, Escherichia coli, and Klebsiella species.
3. Consider outpatient management with a parenteral broad spectrum antibiotic (ceftriaxone) if the child is non-toxic, the family and follow up are reliable, and the child has none of the signs of more serious neutropenia syndromes. Followup in an outpatient setting to check the patient's clinical status, check culture results, and administer a second dose of ceftriaxone.
4. DANGER SIGNS: failure to thrive, inflammatory anemia, thrombocytopenia, splenomegaly, lymphadenopathy, joint swelling/bone pain, dysmorphia, recurrent serious infections, fever/infectious symptoms every 21 days, unusual or resistant infections, periodontal disease. If any of these danger signs are present, patients should have more extensive evaluations and a hematology consultation. If no danger signs present themselves, no further testing is needed and parents should be reassured. The most likely diagnosis in the young child is chronic benign neutropenia.

5. Routine use of granulocyte-colony stimulating factor to increase bone marrow production of neutrophils is not indicated for most acquired neutropenias and should be limited to specific disorders where the neutropenia is due to inadequacy of the marrow reserve pool.

DISORDERS OF NEUTROPHIL FUNCTION

Abnormalities in neutrophil numbers are often recognized on a CBC done for other reasons. Children with neutrophil dysfunction must be suspected on clinical grounds, keeping in mind that even the most common primary neutrophil dysfunction syndrome is extremely rare. Children with primary neutrophil function defects usually present with low-grade chronic bacterial or fungal infections. Skin and mucosal infections, lymphadenitis, and abscesses are among those infections commonly seen. These infections tend to be persistent and difficult to resolve with standard treatment. Bacterial sepsis is an unusual finding at presentation.

Children with suspected immunodeficiency should be screened for humoral, cellular, and complement mediated immunity prior to neutrophil function assays. Screening tests routinely available through reference laboratories include: Complete blood count (note that a decrease in neutrophils and platelets/or red blood cells should raise concerns of leukemia or metastatic tumor in the bone marrow), quantitative immunoglobulins (IgG, IgM, IgA, IgE), antibody titers after vaccination (diphtheria, tetanus, and pneumococcus), B-cell counts/phenotype, delayed-hypersensitivity skin tests (Candida, tetanus, or Trichophyton), T-cell counts/phenotype, and total hemolytic complement assay (CH50).

Once a neutrophil defect is suspected and other causes of primary immunodeficiency are ruled out, referral to a specialist familiar with the evaluation of primary neutrophil defects should be made. Anticoagulated samples (usually sodium heparin) should be freshly drawn and transported as quickly as possible to a neutrophil or immunology laboratory. Control samples and parental blood samples are often requested for comparison purposes. Neutrophil function tests generally need to be performed at research laboratories experienced with the assays. NBT testing for reactive oxygen species is sometimes available through reference clinical laboratories, though often times it is unreliable with high false negative rates when done in this setting. General tests of neutrophil function include tests such as modified Boyden chambers (chemotaxis), nitroblue tetrazolium (NBT) slide test (reactive oxygen species), dihydrorhodamine oxidation by flow cytometry (reactive oxygen species), neutrophil receptor quantitation, and phagocytosis/particle ingestion assays.

Characteristic disorders of neutrophil function include:

1. Chronic granulomatous disease: Pathophysiology is impaired respiratory burst (defective NADPH oxidase); inheritance usually X-linked, some autosomal recessive; 1 in 500,000 prevalence, 1 in 2,000,000 live births, two-thirds< 1 year old at diagnosis; most common infections include pneumonia and lymphadenitis; most common infecting organisms (generally catalase negative) S. aureus, S. marcescens, B. cepacia, and Aspergillus sp.; most common clinical findings are lymphadenopathy, hypergammaglobulinemia, hepatomegaly, splenomegaly, anemia of chronic disease, underweight, chronic diarrhea, short stature, gingivitis, and dermatitis; diagnosis made by NBT, flow cytometry, or cytochrome C reduction; treatment includes prevention of infection with daily trimethoprim-sulfamethoxazole and gamma-interferon three times a week; bone marrow transplantation is experimental but curative.
2. Chediak-Higashi syndrome: Pathophysiology is decreased degranulation, chemotaxis and granulopoiesis; inheritance autosomal recessive; rare with 200 cases reported; multisystem disorder with clinical characteristics that include mild coagulopathy, peripheral and cranial neuropathy, hepatosplenomegaly, pancytopenia, partial oculocutaneous albinism, frequent bacterial infections (usually S. aureus), progressive lymphoproliferative syndrome with death by age 20; diagnosis made by neutropenia, giant lysosomes in neutrophils; treatment includes prevention of infection with daily trimethoprim-sulfamethoxazole and daily ascorbic acid; bone marrow transplantation in accelerated phase.
3. Leukocyte adhesion defect I: Pathophysiology is the lack of an adhesion receptor resulting in impaired chemotaxis, adhesion, and phagocytosis; inheritance autosomal recessive; rare with 60 cases reported; clinically characterized by moderate to severe phenotypes with a lack of pus at sites of infection, delayed separation of the umbilical cord, severe periodontitis and/or gingivitis; diagnosis made by the presence of neutrophilia, decreased neutrophil integrin adhesion receptor (CD11b/CD18) by flow cytometry, and impaired chemotaxis; treatment includes prevention of infection with daily trimethoprim-sulfamethoxazole and bone marrow transplantation if severe.
4. Hyper-IgE (Job's) syndrome: Pathophysiology is a variable chemotactic defect; inheritance autosomal dominant; rare with 50 cases reported; clinically characterized S. aureus pneumonia with pneumatoceles, fungal superinfection of lung cysts, recurrent "cold" abscesses that don't respond to antibiotics, eczema, mucocutaneous candidiasis, coarse facial features, and short stature; diagnosis made by an IgE>2,500 and eosinophilia; treatment includes prevention of infection with daily trimethoprim-sulfamethoxazole and bone marrow transplantation if severe.

Children with neutrophil functional defects rarely present with overwhelming bacterial or fungal infections, but more commonly suffer from low grade, chronic infections that may become indolent and impossible to effectively treat. Chronic infection and inflammation associated with deep seated infections leads to a high rate of morbidity and shortened survival. Low grade infections that are neglected can evolve into serious disseminated infections without the appropriate, timely administration of antibiotics or antifungal agents. Adding to this difficulty in clinical monitoring, is an attenuated inflammatory response that often masks serious infection. Referral to subspecialists experienced in the management of children with immunodeficiencies or neutrophil disorders is critical to minimize morbidity and mortality for this population.

Questions

1. The risk of infection with neutropenia is highest when:
    a. Neutropenia onset is rapid
    b. Low bone marrow cellularity is present
    c. Peripheral destruction of neutrophils is occurring
    d. Anti-neutrophil antibody is present

2. The most common cause of neutropenia is:
    a. Anti-neutrophil antibody
    b. Drugs
    c. Infection
    d. Bone marrow failure
    e. Malignancy

3. Neutropenia associated with steatorrhea is most characteristic of:
    a. Cystic fibrosis
    b. Kostmann syndrome
    c. Evan's Syndrome
    d. Chediak-Higashi Syndrome
    e. Shwachman-Diamond Syndrome

4. Neutrophil defect associated with increased infections with catalase-negative organisms
    a. Hyper-IgE syndrome
    b. Leukocyte adhesion deficiency type I
    c. Leukocyte adhesion deficiency type II
    d. Chronic granulomatous disease
    e. Pseudo-neutropenia

5. Infections in children with defects in neutrophil function are characterized by:
    a. Decreased inflammation that may mask serious infection
    b. Indolent, chronic infections
    c. Bacterial and fungal organisms
    d. Elevated erythrocyte sedimentation rate
    e. All of the above

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Answers to questions

1.b, 2.c, 3.e, 4.d, 5.e

Chapter XII.1. Oncology Treatment Principles
Nu T. Lu

A nine year old boy was treated for pharyngitis one month ago. He is now brought in because his mother notes a decrease in energy, pallor, and easy bruising in his extremities. He complains of leg and arm pains over the last 2 weeks that seem to be aggravated by exercise. He has lost five pounds (2.4 kg) in the past month.

Exam: Vital signs are normal. His height is 130 cm and weight 27 kg (both 25th percentile). He is slightly pale and in no apparent distress. Some palpable nodes are present in the anterior triangle bilaterally. Heart and lungs are normal to auscultation and percussion. The tip of his spleen is 2 cm below the left costal margin and his liver is 3 cm below the right costal margin. His joints have full range of motion and no swelling. His skin shows bruises over the anterior tibial regions and five bruises over the left knee.

Labs: Hemoglobin 7.3. Platelet count 20,000. WBC 42,100 with 86% lymphocytes and 12% atypical lymphocytes. Bone marrow studies confirm B cell acute lymphoblastic leukemia (ALL).

He is treated with a four drug induction chemotherapy which achieves initial remission. Eighteen months later, he relapses requiring an allogeneic bone marrow transplant (BMT). After engraftment, he no longer needs medications or blood product transfusions. Eight months after the BMT, he develops shingles with vesicles on his face. This resolves with appropriate treatment.

Although only 1% of all cancers occur in children (<19 years of age), it is the second leading cause of childhood death. Early detection and prompt therapy have the potential to prolong survival and frequently cure the disease. Many factors are considered in determining the treatment goals for an individual patient: the type of cancer, its stage of growth, the patient's age, and family members' wishes. A team of experts (nurses, social workers, oncologists, surgeons, pathologists, psychologists) tries to meet the complexities of giving the children the most intense course of therapy possible, while not depriving them from having some level of normalcy (going to school, playing with friends).

A variety of modalities are currently employed to treat common malignancies. Surgery, the oldest treatment, provides the best chance of a cure for a localized tumor. It also plays a major role in other aspects of management, including diagnosis, staging, relieving symptoms, reconstruction, and prevention. Yet, its invasiveness physically challenges those undergoing the procedure.

Radiation therapy is used in 2/3 of cancer cases. It induces free radicals to target breaks in DNA, hence interfering with cell proliferation. It is used to treat the primary lesion, shrink a tumor prior to surgery, or palliatively relieve painful symptoms of bone metastasis. Radiation targets rapidly dividing cells, which includes cancer cells and normally dividing cells of the skin, hair, gastrointestinal mucosa, bone marrow, reproductive tissues, sweat glands, and lungs. These correlate with radiation's common side effects: alopecia, nausea, vomiting, pancytopenia, infertility, prostatitis or impotence in males, lung fibrosis and edema. Many of radiation's toxic effects can manifest many years after the treatment. Some examples are: asymmetry of the irradiated extremity, hypothyroidism, neurological dysfunction, growth retardation, and development of a secondary tumor.

Chemotherapy is one of the most common treatments for cancer. It was introduced in the 1940s when Goodman and Gilman first administered nitrogen mustard to patients with lymphoma. Nitrogen mustard, the first alkylating agent used, produced partial remission with considerable toxicity. The era of modern chemotherapy has since evolved to include several other classes of drugs: hormones (prednisone), antimetabolites (methotrexate, 5-fluorouracil), plant alkaloids (etoposide, vincristine, paclitaxel), and antibiotics (doxorubicin, bleomycin). Most of these work by inhibiting some metabolic pathway or DNA synthesis, which ultimately leads to cytotoxicity. Though chemotherapy has limited use for localized tumors, it is often the most effective agent for the management of disseminated or systemic cancer. These include the hematological malignancies (leukemias, lymphomas), metastasis of the primary solid tumor, and potential micro-metastasis after surgery or radiation.

Unfortunately, their utility is limited by the various acute and chronic complications involved with their use. Frequent side effects of chemotherapy include vomiting, diarrhea, cachexia, bone marrow suppression, and immunosuppression. Vomiting and diarrhea lead to fluid loss that often result in hyponatremia. Hyponatremia is also worsened by SIADH. Bone marrow suppression leads to anemia, thrombocytopenia, neutropenia, and hyper-leukocytosis (this is an abnormal increase of white blood cells while the others are an abnormal decrease of different blood precursor cells). Immunosuppression can increase the rate of tumor growth, promote graft versus host disease (GvHD), and predispose patients to opportunistic infections. In addition, the substantial break down of tumor cells by chemotherapy can lead to tumor lysis syndrome, in which a large amount of phosphate, potassium, and uric acids are released into the circulation, when large number of cancer cells are killed.

Supportive care is therefore essential with chemotherapy. Hyponatremia can be corrected by limiting fluid intake, diuresis, or demeclocycline, an ADH antagonist. Vomiting may be prevented by metoclopramide, some H1 antihistamines (diphenhydramine), 5-HT3 inhibitors (ondansetron, granisetron and dolasetron), phenothiazines, dronabinol (marijuana active ingredient), as well as corticosteroids (dexamethasone). Patients undergoing chemotherapy often have a decreased appetite and consequently are malnourished. Enteral tube feeding and parenteral hyperalimentation may become necessary when oral intake is severely inadequate.

Myelosuppression can be treated with transfusion of packed red blood cells, platelet infusions, leukapheresis, or granulocyte-colony stimulating factor (G-CSF). Graft versus host disease may be prevented by irradiating all blood products. Febrile neutropenia may require G-CSF as well as empiric broad spectrum IV antibiotics.

In situations of continual febrile illness for more than 1 week, fungal and viral infections must be considered. Common opportunistic infections include candidiasis, aspergillosis, and Pneumocystis carinii. Temporary prophylactic treatment with trimethoprim/sulfamethoxazole is often prescribed in anticipated bone marrow suppression. Children on chemotherapeutic protocols are prone to complications from disseminated viral infections. They should not be given live attenuated vaccines, since these attenuated organisms may still cause disseminated disease in immunocompromised hosts. Children who are exposed to chickenpox during their chemotherapy should be given IV varicella zoster immunoglobulin. If clinical symptoms develop, hospitalization and IV acyclovir should be instituted.

Although the acute complications of chemotherapy are relatively manageable, some of its long-term consequences are devastating and often cause significant morbidity and mortality. Irreversible complications include leukoencephalopathy following high-dose intrathecal methotrexate, infertility in male patients treated with cyclophosphamide, myocardial damage from anthracyclines, pulmonary fibrosis after bleomycin, pancreatitis after asparaginase, and hearing loss associated with cisplatin. Chemotherapy or radiation may also cause the development of a secondary tumor. There is a 0.5% risk after the first year, but it increases to 25% 12 years after treatment. It is strongly recommended that children be checked annually post chemotherapy to detect a secondary malignancy.

Most of the chemotherapeutic complications result from their nonspecific targeting of both malignant and normally dividing cells. Hence, the newer tumor specific-agents, antisense messenger RNA, anti-angiogenic agents (angiostatin and endostatin), anti-angiogenic monoclonals attempt to overcome some of the side effects of the older chemotherapeutic agents. One of the huge advantages of newer agents is their minimal degree of dose-limiting toxicities. Clinical trials of these agents are currently underway.

Stem cell transplantation has revolutionized the therapeutic options for primary bone marrow diseases and systemic neoplasms. Both autologous and allogeneic transplants have been employed successfully for a variety of hematological and oncological conditions in which chemotherapy and/or radiation have failed to induce remission. Examples include juvenile myelomonocytic leukemia, acute lymphoblastic leukemia (ALL), acute myeloid leukemia in first or second remission, chronic myelogenous leukemia, severe combined immunodeficiency, hemophagocytic lymphohistiocytosis, aplastic anemia, Diamond-Blackfan anemia, beta-thalassemia major, and some inborn errors of metabolism.

Perhaps, the most challenging aspect of peripheral blood stem cell transplantation (PBSC) is finding a donor with sufficiently matching HLA haplotypes (i.e., chromosome 6, which encodes HLA). To minimize rejection and GvHD, more rigorous conditions, with serological as well as molecular matches, are now required to ensure closer HLA match. Once donors are identified, they are treated with G-CSF or GM-CSF (colony stimulating factors) to increase the proliferation of precursor stem cells. Collection of stem cells is made at various sites in the body: bone marrow, peripheral blood, and sometimes even cord blood.

Despite great efforts to match HLA genotypes, stem cell transplant is currently not widely used. Its limitations still include the non-availability of the "right" donors, concern about the lack of randomized comparisons to less risky chemotherapy in certain diseases where chemotherapy alone may induce remission, and chronic graft versus host disease. Certain measures may be instituted to decrease the prevalence and severity of GvHD. The combination of cytotoxic drugs such as methotrexate with inhibitors of T cells activation such as cyclosporin and FK 506 has dramatically reduced the severity of both acute and chronic GvHD. In addition, depletion of donor T-cells essentially eliminates GvHD. However, donor immunosuppression inadvertently increases the risk of infections and decreases the graft versus leukemia response that may lead to the higher relapse rate in these cases. Hence, it is a fine balance between the absolute prevention of GvHD and the risk of relapse.

Pain management, an essential component of oncological therapy, has recently become a focus of attention. Children were once believed to not feel as much pain because of their underdeveloped nervous system. However, cancer causes tremendous pain in children. Prolonged pain saps spiritual energy and diminishes the body's ability to heal. Pain therefore should be managed in a stepwise fashion, and should be a top priority for any oncological patient, especially those needing palliative care.

The magic bullet is hard to come by. The major challenge in oncology treatment is to find the right combination of type and amount of chemotherapy, right amount of radiation, and the best timing of stem cell transplantation for each individual patient. Future therapeutic approaches include immunotherapy as well as gene therapy. Immunotherapy can be viewed as fine-tuning of the GvHD reaction in order to have it work towards the body's advantage to fight against cancer. In several animal models, it has been successfully proven that the immune system can be an important component in fighting off cancer. The immune system provides high precision in selectively targeting cancer cells. If there is some means to engraft a competent immune system to a leukemic patient, it hopefully will stimulate an immune response against leukemic cells. Several research groups have tested interleukins, notably IL-2 and IL-4, which stimulate both T and B-lymphocytes in ways that theoretically inhibit tumor growth. Other interleukins, IL-6 and IL-10, promote the development of B cell malignancies because they inhibit the synthesis of antiviral cytokines (interferons) and IL-2. Future drug development may consider inhibiting these tumor-promoting compounds.

Gene therapy is an exciting possibility for essentially curing cancer. The principle behind this approach is that cancer is inherently a genetic defect. Hence, if it is possible to use a vector to carry the good genes to target the malignant cells, the deposit of the good genes into cancerous cells may lead to tumor regression. Gene therapy is still in the study phase.

Questions

1. What are some common opportunistic infections associated with immunosuppression induced by chemotherapy? What is the appropriate prophylaxis for these patients?
2. Give an example of a drug from each of the five classes of current chemotherapy in use.
3. What is a serious side effect for methotrexate use especially intrathecally delivered?
4. What is the mechanism responsible for most chemotherapeutic complications?
5. Where are various places that stem cells may be harvested from in the body?

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Answers to questions

1. Common infections include candidiasis, aspergillosis, and Pneumocystis carinii. Prophylactic treatment with trimethoprim/sulfamethoxazole is indicated.
2. Hormones (prednisone), antimetabolites (methotrexate, 5-fluorouracil), plant alkaloids (etoposide, vincristine, paclitaxel), antibiotics (doxorubicin, bleomycin), anti-angiogenesis drugs.
3. Leukoencephalopathy
4. Most of these work by inhibiting some metabolic pathway or DNA synthesis, which ultimately leads to cytotoxicity
5. Bone marrow, peripheral blood, and sometimes even cord blood.

Chapter XII.2. Leukemia and Lymphoma
Bruce T. Shiramizu, MD

This is a 10 year old boy who presents to the emergency department with a chief complaint of fever and increasing tiredness. He was well until 2 weeks ago when he had an upper respiratory illness (URI). He has been tired with decreased activity since the URI, and has missed school and sports practices for 2 days. He has a decreased appetite and has lost 2 pounds over the last 2 weeks. He has some shortness of breath when he climbs stairs, but his parents deny cough, fever, nausea, emesis, bruising, headache, or visual problems. His past medical health, including birth history, immunizations, and other medical problems is unremarkable. He lives with his two parents and 6 year old brother, all of whom are healthy. The sibling and parents had similar URI symptoms 2 weeks ago, but everyone else is back to normal activity levels. There is no family history of relevant medical problems.

Exam: VS T 38.5 degrees C, P 120, R 32, BP 110/56. Height & weight at the 80th percentile. He is alert, tired and slightly pale appearing, but in no apparent distress. His head is normocephalic without scalp lesions. His hair texture is normal. His ear canals and TMs are normal. Pupils are equal and reactive to light. Conjunctivae are pale. His fundi are normal. His nasal passages are clear. His mucous membranes are dry and pale. His posterior pharynx is erythematous without lesions and no tonsillar enlargement. His dentition and gums are normal. No nuchal rigidity is present. He has bilateral cervical nodes, posterior cervical nodes, axillary nodes, and inguinal nodes palpable (about 1-2 cm), mobile and nontender. His chest exam (breasts, lungs, heart) is normal except for some tachycardia. His abdomen is flat and non-tender with normal bowel sounds. His liver edge is palpable at the costal margin. His spleen is palpable 4 cm below the left costal margin. His back is normal. His skin shows no lesions, bruises or petechiae. Upper and lower extremities are normal. His neurological exam is normal.

Laboratory: CBC Hgb 7, Hct 24, MCV 100, WBC 56,000, Differential 14% lymphoblasts, 80% lymphocytes, 6% atypical lymphocytes. Platelets 23,000. Chest x-ray shows clear lung fields but a wide mediastinum.

He is admitted to the hospital and a diagnostic workup including a bone marrow aspirate and biopsy reveals acute lymphoblastic leukemia.

There are different types of leukemia but the most common leukemia that occurs in children is acute lymphoblastic leukemia (ALL). ALL is the most common cancer in children representing 23% of cancer diagnoses among children younger than 15 years of age and occurring at an annual rate of approximately 31 per million (1). Approximately 2,400 children and adolescents younger than 20 years of age are diagnosed with ALL each year in the USA. There is a sharp peak in ALL incidence among children ages 2 to 3 years. Lymphomas, in general, are divided into two broad categories, Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). As a group, it is the third most common childhood malignancy with HD and NHL accounting for approximately 10% of cancers in children less than 20 years of age (2). In the United States, there are about 800 new cases of NHL diagnosed each year. Incidence is approximately 10 per 1,000,000.

For both ALL and lymphoma (HD and NHL), the signs and symptoms may be similar but non-specific. The clinical manifestations may present insidiously or acutely, as an incidental finding on a routine complete blood count analysis or as a life-threatening infection or respiratory distress. Some characteristics which may present at the time of diagnosis are lethargy, fever, joint pain, bleeding, abdominal pain, CNS manifestations, and/or difficulty breathing secondary to a mediastinal mass. On physical examination, there may be pallor, hepatosplenomegaly, petechiae, and/or lymphadenopathy.

Because some rare cases may be difficult to diagnose even with proper diagnostic biopsies, other diagnoses should be entertained. These include viral infections such as Epstein-Barr virus, cytomegalovirus; other malignancies such as neuroblastoma; hematological disorders such as aplastic anemia, histiocytosis, idiopathic (immune) thrombocytopenic purpura (ITP); and juvenile rheumatoid arthritis. In general, the differential diagnosis between ALL and NHL has been debated for years, and the criteria utilized to distinguish between the two categories of diseases have been arbitrary. While both entities can be of B-cell or T-cell phenotype, the distinction between NHL and ALL is currently based on the degree of bone marrow involvement. Children who have more than 25% infiltration of their marrow with blast cells are considered to have ALL.

Treatment and management of ALL and NHL are based on proper diagnosis and staging to determine the extent of disease involvement. Diagnosis is made from either the bone marrow (ALL) or tissue (NHL), and includes immunophenotyping, cytogenetics, flow cytometry, and/or molecular studies such as gene rearrangements. Recommended staging studies include a careful physical examination, complete blood count, bone marrow aspirate or biopsy, lumbar puncture, and radiographic studies including possible nuclear medicine studies to assess the extent of disease.

Prior to instituting specific therapy, measures should be instituted to treat emergent problems, particularly in patients with advanced disease and who may have associated airway compression or superior vena cava obstruction. Measures should also be in place to be able to monitor and intervene for treatment related problems such as tumor lysis. Tumor lysis can occur spontaneously or as a result of chemotherapy leading to serious metabolic complications such as hyperuricemia, hyperkalemia, and hyperphosphatemia. This could ultimately lead to renal failure or cardiac arrest if left untreated.

Successful treatment of children with ALL and NHL requires the control of systemic disease (marrow, liver and spleen, lymph nodes, etc.) as well as the treatment (or prevention) of extramedullary disease particularly in the central nervous system (CNS) (1,3). The main goal of therapy is to begin induction treatment as soon as the diagnosis is made in order to obtain remission. After inducing remission, the next goal is to maintain remission. In general, therapy is based on cytotoxic drugs affecting the rapidly dividing cells during the cell cycle. Multiple drugs are used because each class of drugs acts on a different part of the cell cycle with the intent of interrupting cell division in the majority of malignant cells. The concept of inducing remission initially is to try and rapidly destroy the majority of malignant cells within the first 30 days of treatment. Ongoing and subsequent treatment strategies are based on the concept that malignant cells that "escaped" the induction phase will enter the cell cycle over a period of time and will then be affected by the drugs. Most of the drugs are administered orally, intravenously, or intramuscularly. CNS treatment and/or prophylaxis is administered via a lumbar puncture (intrathecal). Occasionally, emergency treatment has to be considered for life-threatening situations such as airway compression, spinal cord compression, etc. This can be accomplished with the use of radiation to the involved sites. The immune system is compromised throughout the duration of therapy. Therefore one must be attentive to any signs or symptoms of septicemia. Additionally, exposure to infectious agents including live vaccines should be avoided.

In general, there are clinical and laboratory findings present at the time of diagnosis which may correlate with prognosis. A high tumor burden, whether assessed by total white blood cell count for ALL or high stage disease in NHL (or elevated serum LDH) has been

consistently found to be an important prognostic factor. Other factors might include specific chromosome abnormalities, age, race, or gender. Recently, the rapidity of response to induction therapy or the presence of residual disease has been examined as a predictor of outcome.

Approximate 75-80% of children and adolescents with ALL and NHL will survive at least 5 years with modern chemotherapy although outcome is variable depending on a number of factors. Since nearly all children will achieve remission with proper treatment, one of the main obstacles today is how to effectively treat bone marrow or CNS relapses. Other challenges are the result of successful treatment and related to screening and treating long term complications from therapy. These include CNS sequelae affecting cognition and learning, growth failure, reproductive sequelae, cardiac sequelae, and secondary malignancies.

Questions

1. You are called to the ER to evaluate a 10 year old boy who has been tired for 2 weeks and his parents noticed that he becomes short of breath when he walks upstairs to go to his bedroom. Upon your physical exam, you note that he has some shortness of breath when he is placed in the supine position. Which of the following procedures might you consider initially ?

a. Arrange for a better examination of the lungs and possible diagnostic biopsy under general anesthesia.

b. PA and Lateral chest x-ray.

c. An MRI of the chest to rule out an enlarged heart.

d. Diagnostic fine needle aspirate without general anesthesia to find out why he is short of breath.

2. One of your patients (5 year old female) was diagnosed with ALL 6 months ago and is being treated by a pediatric hematologist/oncologist with chemotherapy. She now wants to start back to school and the school administration tells the parents that she needs to be up to date on her immunizations. They would like her MMR administered. What advice do you offer them?

a. Even though the child is on chemotherapy, there is evidence that her immune status is competent, therefore she can be given all of her scheduled immunizations.

b. Her immune system will only mount an immune response to live, attenuated vaccines, therefore she can receive the MMR vaccine as scheduled.

c. MMR vaccine is contraindicated in a child receiving chemotherapy for cancer.

d. The parents should wait until the child recovers from the side effects of the current cycle of chemotherapy and then make an appointment for the MMR vaccine.

3. As the pediatrician of a 7 year old boy who was diagnosed with NHL at 4 years of age and successfully completed chemotherapy, the parents made an appointment to have him see you because they were advised by the boy's teacher that he has not been keeping up academically. You review the boy's medical history, and other than the chemotherapy, you do not see anything that would account for the poor school performance. What is the best advice to the parents?

a. You remind the parents that because of the child's past medical situation, he has a feeling of neglect and abandonment therefore will need some remedial attention to overcome the psychological condition, which is causing his poor academic performance.

b. There is a high likelihood that the child has a secondary brain tumor, and may need at CT scan of the head.

c. Having received therapy which compromised the child's immune status, he most likely has meningitis, therefore should be admitted for therapy.

d. Children who have received chemotherapy and/or radiation may experience delays in growth and development, therefore further testing and gathering of information should be suggested.

4. You are the primary pediatric resident on the hematology/oncology team and covering the service over the weekend. A 6 year old was admitted on Thursday, with a history of being tired, shortness of breath, pallor and weight loss. A prompt and efficient workup revealed a diagnosis of T-cell NHL. Following the family conference and consent process to begin the child on a lymphoma protocol, treatment was started by the weekend. The chemotherapy is being administered properly, with attention to tumor lysis precautions, including vigorous hydration. As you make your midnight rounds, you notice that the documentation of fluid input and output shows a large discrepancy. The amount of fluid administered (orally and intravenously) is almost twice the volume as the urine output. You suspect that the patient is experiencing complications from the chemotherapy and think you should do which of the following:

a. Increase the hydration because the fluid balance is not equal, and the patient should be receiving more than twice maintenance fluid intake during induction chemotherapy.

b. Perform a thorough physical exam, have the patient weighed, repeat the serum electrolytes immediately to determine if the patient is fluid overloaded.

c. The patient is experiencing renal failure, and needs immediate consultation by a nephrologist to begin dialysis.

d. You decide that the oral fluid intake has not been taken into consideration, which it should be, and estimate the amount the patient has been taking in orally based on what was served on his meal trays. By your calculations, the total fluid intake and output is equal, therefore no further action is needed.

5. The parents of a 5 year old boy bring their son to see you because they are concerned that their son has leukemia. His 3 year old sister had a URI 2 weeks ago, but fully recovered and has been back in school and active. This 5 year old boy has URI symptoms now. They noticed bruising on his legs and arms over the last few days, and their neighbor's daughter had similar findings 2 years ago before she was diagnosed with acute lymphoblastic leukemia. The mother's grandfather died at the age of 80 from leukemia. Your physical exam is unremarkable except for the bruises noted on the anterior legs and on the forearms. He is playful and cooperative. What course of action or advice should you do next?

a. Because of the strong family history of ALL and the leukemia case in the neighborhood, you should pursue a presumed workup of ALL and notify the state Cancer Control Division.

b. Obtain a complete blood count.

c. The bruising strongly makes you suspicious of possible child neglect or abuse. Reassure the parents that you do not suspect them, but you should alert them of your concerns and find out who could possibly be the perpetrator.

d. Since the bruises are the only abnormal finding, you are less concerned about leukemia, therefore you alleviate the parents' concerns and tell them that the bruising is most likely related to the child's aggressive activities at school.

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Answers to questions
1. b. The fact that the child is short of breath in the supine position could be related to a mediastinal mass, which can be identified on a chest x-ray. A mediastinal mass could be a potential emergency situation, therefore a chest x-ray should be considered shortly after the history and physical exam are completed.
2. c. Live vaccines are contraindicated throughout the treatment course due to the immunocompromised status of the patient.
3. d. Delays in growth and development may occur as a result of chemotherapy and/or radiation therapy.
4. b. The chemotherapy may have induced tumor lysis causing hyperuricemia, which in turn may be affecting the kidneys.
5. b. As part of the differential diagnosis, you should consider ITP.

Chapter XII.3. Solid Tumor Childhood Malignancies
Christina Keolanani Kleinschmidt

An 18 month old female presents to the office for her well-child examination. A third year medical student is allowed to take the history and perform the initial examination. On a routine ophthalmoscopy exam, the student notices that the child does not have a red reflex in the right eye. This is reported to the physician who confirms the exam finding. There is no history of weight loss, anorexia, crossed eyes, fever, or irritability.

Exam: VS T 37.0, P 110, R 26, BP 92/42. Height, weight, head circumference are all at the 40th percentile. She is alert and active. Leukocoria is present in the right eye. A normal red reflex observed in the left eye. Pupils are equal and reactive. The eyes are conjugate. Facial function is good. The remainder of the physical examination is negative.

Clinical Course: The child is referred to an ophthalmologist. An ophthalmoscopy exam performed under general anesthesia reveals a tumor in the posterior pole of the right eye. An orbital CT demonstrates that the tumor is confined to the globe (i.e., no spread outside the eye). Since the tumor is small it is treated with laser photoablation. Careful follow ups are scheduled to monitor for recurrences or development of secondary tumors.

This chapter will cover the four most common malignant solid tumors of childhood: retinoblastoma, osteosarcoma, neuroblastoma and Wilms' tumor.

Retinoblastoma

Retinoblastoma is a slow growing malignant tumor of the retina that may be confined to the eye for up to months or even years. In the United States it is the seventh most common pediatric malignancy (1). About 90% of cases occur before the age of 5. Bilateral tumors occur at an earlier age than unilateral tumors. The mean age of diagnosis in bilateral tumors is 12 months whereas unilateral tumors occur at a mean of 24 months of age (2).

The exact molecular pathogenesis has been elucidated for retinoblastoma, which results when there is a mutation in the retinoblastoma gene found on the long arm of chromosome 13 at band 14 (13q14). The gene is a tumor suppressor gene that is involved in regulating the cell cycle. In order for retinoblastoma to manifest, both Rb alleles must be mutated (the essence of the two hit hypothesis). In the hereditary form of retinoblastoma, the individual inherits a mutant Rb gene from the germ line. Another mutation must occur in a somatic retinal cell in order for retinoblastoma to manifest itself. In the nonhereditary form, both mutations must occur in the same somatic retinal cell. When both are mutated, defective intracellular transcription and unchecked cell proliferation leads to malignant transformation (3).

If it is not detected during the routine ophthalmoscopic exam or suspected due to family history, the first presenting sign may be a white pupillary reflex called leukocoria, which is frequently noted on flash photography as a white reflex instead of the usual flash photography "red eye". Parents will often notice this and bring this to the attention of the child's physician, usually after a significant delay. This sign is present in approximately 60% of the patients and is attributed to the formation of a central posterior pole tumor. Another 20% may present instead with strabismus due to tumor involvement of the macula. Retinal detachment may also be detected. The patient may also present with a red, painful eye, poor vision, unilateral pupil dilation, heterochromia (the iris color of each eye are not the same), or nystagmus. If the tumor is in an advanced stage, the patient may present with constitutional symptoms and signs as well as neurologic defects, orbital mass, proptosis, or blindness (1).

Leukocoria is difficult to detect during a routine exam. If it is not detected during the exam, yet the parent reports an abnormal pupil, a referral should still be made to an ophthalmologist. Ophthalmoscopy done by a specialist through dilated pupils is the most important test performed to diagnose retinoblastoma. If the child is young, this must be done under general anesthesia. Parents and siblings should also have a dilated ophthalmoscopic examination to rule out unsuspected or dormant tumors (2). A CT scan can also be used to detect intraocular calcification, optic nerve involvement, and extraocular extension of the tumor (4).

Careful examination is required to rule out any other disorders that resemble retinoblastoma. The differential for a mass should include astrocytic hamartomas and granulomas of Toxocara canis, Coat's disease, retinopathy of prematurity, and persistent hyperplastic primary vitreous should be suspected when there is retinal detachment (1).

Treatment options for retinoblastoma include enucleation, external beam radiation, plaque radiation, laser photoablation, thermotherapy, cryotherapy, and chemotherapy. The choice of treatment will ultimately depend on the size, location, and extent of the tumor, whether it is bilateral or unilateral, if there is visual potential, or if extraocular disease or metastasis is present.

Enucleation is performed on large unilateral tumors that have led to severe visual impairment. Individuals with optic nerve invasion, secondary glaucoma, and seeding into the pars planta have also undergone enucleation (5). In the past, enucleation was performed on the eye with the most advanced disease in bilateral tumors. However, chemotherapy and local therapy have successfully replaced this practice (2).

In the past, standard therapy for the least involved eye in bilateral tumors has been external beam radiation. However, long term consequences such as cataract formation, radiation retinopathy, optic neuropathy, and the development of secondary tumors has lead to the search for alternative treatments. Radioactive plaque therapy (or brachytherapy, in which radioactive seeds are implanted close to the tumor) has since been employed to restrict the area of the orbit exposed to radiation. This procedure has reduced the harsh consequences of radiation. Brachytherapy has also been used to treat unilateral tumors. Small tumors have also responded well to other types of local therapy, in particular cryotherapy and laser photoablation (5).

Chemotherapy is also a common therapy used in the treatment of retinoblastoma. In the past, it was used basically to treat advanced extraocular disease. Today, it is used when there is extraocular extension, metastasis, and positive cerebrospinal fluid findings. It is also used if accidental dissemination of tumor cells has occurred. For example if a previous intraocular procedure was done before the diagnosis of retinoblastoma was made, the patient may be treated prophylactically with chemotherapy (5).

The extent of optic nerve involvement, extension of the tumor, and choroidal involvement directly influences mortality. The outcome has been excellent in individuals suffering from unilateral intraocular tumors. Individuals with optic nerve extension beyond the lamina cribrosa have only a 40% 5 year survival rate (4). A cure rate of greater than 90% has been seen after enucleation of unilateral intraocular tumors. The use of local ablation with or without chemotherapy is also usually successful (3).

Patients with a germ line mutation of the Rb gene fare a worse outcome. These are individuals who were born with one mutant Rb gene and sustained a subsequent spontaneous mutation in a somatic Rb gene. They have poor survival rates and have a reduced likelihood of salvage of vision. If they survive retinoblastoma they are at an increased risk for developing a secondary cancer. More than 90% will develop a secondary cancer within 32 years after treatment (1). This is because the retinoblastoma gene is linked to nonocular tumors, most notably osteosarcoma (1).

Osteosarcoma

Osteosarcoma is a malignant mesenchymal tumor of bone with resultant osteoid formation. It is the third most common cancer in children and adolescents (6). It has a bimodal incidence with the first peak occurring in the second decade of life and the second peak occurring in the elderly. It is more common in boys than in girls. The common sites of involvement are the metaphyseal regions of the distal femur, proximal tibia, and proximal humerus (7).

The exact cause of osteosarcoma is unknown, but it has been linked to a variety of syndromes and genetic changes. Most notably, it has been strongly correlated with a germ line mutation of the Rb gene. Patients with retinoblastoma have a significantly increased risk for the development of osteosarcoma. If these individuals were treated with radiation, their susceptibility increases further (7). Alkylating agents and other antineoplastic drugs, have also been reported to increase the risk of developing this neoplasm. Individuals suffering from Li-Fraumeni syndrome, a familial cancer syndrome associated with a germ line mutation, are also predisposed (8).

Patients usually present with pain and swelling most commonly at the knee. The pain may be intermittent and most commonly occurs at night causing it to be often dismissed as growing pains. Since individuals afflicted with this disease are commonly going through their "growth spurt", this conclusion seems rational. It may further be mistaken by the patient as a sports injury. However, not all patients present with a history of trauma. Physicians must take care not to make the same assumptions. Additional clinical findings may help them distinguish this disease from benign growing pains. These findings include a palpable mass, limited range of motion, tenderness, and warmth (8). However, since none of these findings may be present initially, an imaging study is often necessary to diagnose osteosarcoma during its earliest stage.

The diagnosis of osteosarcoma can be made on: x-ray of the affected bone, MRI, CT scan, radionuclide bone scan, and biopsy. Radiographs may display a mixed lytic and blastic lesion. In more advanced cases, a sunburst pattern of new bone formation and lifting of the bony cortex may create what is called a Codman triangle (4). An MRI of the lesion and the entire bone is done to evaluate the tumor's proximity to nerves and blood vessels as well as its extension into a joint or soft tissue. CT of the chest, and bone scintigraphy detects sites of metastasis (6). After all of these procedures are done, a biopsy can be performed to make the definitive diagnosis. Together, these procedures should help to differentiate osteosarcoma from other bone disorders such as histiocytosis, Ewing's sarcoma, lymphoma, and osteomyelitis (8).

In the past, osteosarcoma was treated with surgery alone. However, the survival rate was poor even for nonmetastatic cases, since most patients have non-detectable micrometastases at presentation. Surgical treatment combined with chemotherapy has greatly improved the survival rate. Treatment options available today include chemotherapy, amputation, and limb salvage procedures (7).

Previously, surgical treatment meant amputation of the affected bone. The bone would be amputated 7 cm proximal to the proximal border of the tumor to minimize recurrence. The patient would then undergo chemotherapy. However, with the advent of even more effective chemotherapeutic agents, limb salvage treatment is the new therapeutic approach to osteosarcoma. The patient undergoes preoperative chemotherapy to induce primary tumor necrosis and treat micrometastatic disease (6). A block excision of the tumor and prosthetic replacement is then performed (7). Contraindications for limb salvage therapy include involvement of a neurovascular bundle by the tumor, immature skeletal age (especially for the lower limb), infection in the region of the tumor, and extensive muscle involvement that would result in poor functionality (4).

This multi-agent approach has greatly improved survival rates. Approximately 75% of patients with nonmetastatic osteosarcoma of the extremity are cured. Even individuals with lung metastases have shown a 20% to 30% cure rate when treated aggressively with chemotherapy and resection of lung nodules (8). This is an improvement because pulmonary metastasis has been the major obstacle in curing patients with osteosarcoma.

Neuroblastoma

Neuroblastoma is a neoplasm of childhood that arises from neural crest cells involved in the development of sympathetic nervous tissue. It is the most common extracranial solid tumor of childhood, occurring at a rate of 1 case per 10,000 persons. Young children are the primary targets, with the median age of diagnosis occurring at 2 years of age. It rarely occurs in children over 10 years of age and it has a slight predilection for boys (2).

The exact cause of neuroblastoma is unknown, but it has been associated with various disorders and mutations. It has been tied to disorders that involve neural crest development such as Hirschsprung's disease and neurofibromatosis type I. It has also been linked with

several different types of genetic changes. These changes include n-myc proto-oncogene amplification, chromosome 1p deletion and chromosome 17q gain (9). It is believed that the 1p deletion and 17q gain are the result of an unbalanced translocation between these two sites (10). The exact role of these changes in the pathogenesis of neuroblastoma has not been elucidated.

Neuroblastoma develops from sympathetic neuroblasts anywhere along the sympathetic chain ganglia or in the adrenal medulla. Spontaneous malignant transformation is believed to occur when sympathetic neuroblasts fail to differentiate. When there is complete failure of differentiation, a neuroblastoma forms.

Primary tumors occur 50% in the adrenal gland, 30% in retroperitoneal sympathetic ganglia, and 20% in cervical and thoracic ganglion (9). The patient's clinical presentation depends on the location of the primary tumor, the size of the tumor, and if it has metastasized. The typical constitutional symptoms of cancer, fever, general malaise, and pain, are present. Complicating the patient's clinical presentation is the fact that approximately 75% of patients will present with metastatic disease at the time of diagnosis. Common sites of metastasis are lymph nodes, bone marrow, liver, skin, orbit, or bone (especially facial bones, skull, and appendicular bone) (2).

Adrenal and retroperitoneal tumors present as an abdominal mass extending from the flank to the midline of the abdomen. The mass is usually firm, irregular, and nontender. If the mass begins to enlarge and extend further in the cavity, abdominal distention, anorexia and weight loss occur. The mass may also be a result of hepatomegaly due to tumor metastasis, so physicians must take care not to miss this diagnosis. Retroperitoneal tumors may extend into the paraspinal area and compress on the spinal cord. Thoracic tumors may compress the spinal cord and cause paraplegia. Lower lumbar tumors may cause cauda equina syndrome (10).

Thoracic and cervical ganglion may also compress on surrounding structures. Thoracic masses may be an incidental finding on a chest x-ray done to evaluate dyspnea or other upper respiratory problems. A cervical tumor presents as a hard, fixed mass associated with Horner's syndrome or tracheal compression (10). These patients may present with myosis, ptosis, anhydrosis, flushing, and apparent enophthalmos.

On the initial visit, the patient may also present with bone or ocular problems that indicate metastasis to these regions. The bone metastasis may manifest as bone pain with refusal to walk and reported tenderness, swelling, or the finding of a localized lump. If the tumor extends into the marrow, bone marrow suppression may occur. This manifests as anemia and weakness. Periorbital metastasis is associated with orbital ecchymosis and proptosis, also described as "raccoon eyes" (10).

Clinical manifestations may also be a result of substances released from the tumors. Release of vasoactive intestinal peptide (VIP) may cause intractable secretory diarrhea leading to hypokalemia and dehydration. Release of catecholamines from the tumors is rare and may cause hypertension, tachycardia, palpitations, profuse sweating, and flushing (9). Another mysterious syndrome associated with neuroblastoma is opsomyoclonus (also called opsoclonus). This syndrome consists of myoclonic jerks and random eye movements sometimes associated with cerebellar ataxia. It is sometimes called the dancing eyes and dancing feet syndrome because of its physical presentation. The exact mechanism is unknown but hypotheses implicate either a peptide produced by the tumor or immunologic cross reactivity between the tumor and cerebellar neurons (10).

Bone pain may resemble symptoms seen in rheumatoid arthritis, rheumatic fever, osteomyelitis, and acute leukemia. Abdominal masses are also present in Wilms' tumor, lymphoma, mesenteric cysts, hydronephrosis, and splenomegaly. Intractable diarrhea may be due to malabsorptive states (11).

If the historical and physical findings lead to the suspicion of neuroblastoma, a complete blood count, urinalysis, and imaging studies should be done. A CBC may show anemia and thrombocytopenia indicating extension into the bone marrow. Special urine chemistry may pick up catecholamine metabolites such as homovanillic acid (HVA) and vanillylmandelic acid (VMA), break down products of the catecholamines secreted by the tumor. The skeletal survey may discover bone metastases. MRI may also detect bone metastases as well as intraspinal tumors (11). At initial presentation, ultrasound is useful for diagnosing intra-abdominal tumors and can display calcifications (11), but ultrasound interpretation requires skilled expertise. Falsely negative studies are misleading for the clinician unless an alternate imaging study such as a CT scan is done to make the diagnosis.

The diagnosis must be confirmed by histologic examination. Neuroblastoma is known as one of the small, blue, round cell tumors of childhood. Histologically, it is characterized by undifferentiated neuroblast aggregates that are separated by fibrovascular septae. Neuroblastomas that mature into benign ganglioneuromas due to spontaneous regression or therapy-induced maturation may have a mixture of undifferentiated and differentiated cells (10). Some neuroblastomas (especially in infants) may undergo spontaneous regression, even if widely disseminated at initial presentation.

Treatment depends on the stage of the tumor and its histology. Surgical resection is the primary treatment for those who have a localized tumor that is resectable. This includes patients with tumors that are localized to one side of the midline or those which cross the midline without encasement of major blood vessels. Radiation is indicated in those with localized, unresectable tumors that have not responded to initial chemotherapy. Chemotherapy is used in patients with advanced stages of neuroblastoma (2).

The main prognostic factors for neuroblastoma are the age of the patient, the stage of the disease, presence of n-myc amplification, and chromosome 1p deletion. Children who are younger than 1 year old and have favorable histology have better survival rates for all stages than those older than 1 year. For example, a child older than 1 year with stage 2 disease has an 85% disease-free survival whereas a child younger than 1 year with stage 2 disease has nearly a 95% disease-free survival (10).

Wilms' Tumor

Wilms' tumor is a malignant embryonic neoplasm of the kidney most commonly seen in young children. It is the second most common abdominal tumor in children (neuroblastoma is more common). It peaks at ages 1 through 3 years with the median age of diagnosis occurring at 3.5 years in those with unilateral involvement (13). Bilateral involvement presents at an earlier age than unilateral involvement.

The exact cause of Wilms' tumor is unknown, but mutations in the short arm of chromosome 11 have been detected in approximately 30% of the patients (15). The Wilms' tumor suppressor gene (WT1) is located on locus 11p13 and acts to regulate transcription of other genes during normal renal development (16). Mutation of WT1 predisposes an individual to nephrogenic rests, benign clusters of blastemal and stromal cells, which may be subjected to further mutation leading to malignant transformation (2). Deletion of this locus has been linked to the WAGR (see below) and Denys-Drash syndromes. These are syndromes that consist of various congenital anomalies in conjunction with Wilms' tumor. Individuals with the WAGR syndrome present with Wilms' tumor, aniridia, genitourinary malformations, and mental retardation (15). Those who suffer from Denys-Drash syndrome have Wilms' tumor, nephropathy, and genital abnormalities (15).

A second locus has recently been discovered at the 11p15 locus. It is denoted as the WT2 gene, but its exact functions have not been elucidated. Some hypothesize that the gene is actually IGF2 (insulin growth factor 2), which encodes for a growth factor found in

abundance in Wilms' tumor (2). The Beckwith-Wiedemann syndrome has been linked to this locus. Patients with Beckwith-Wiedemann syndrome display organomegaly (liver, kidney, adrenal, and pancreas), macroglossia, omphalocele, and hemihypertrophy (15). Individuals with this syndrome have a 10-20% incidence of tumor development, including Wilms' tumor (16).

This neoplasm most commonly presents as an asymptomatic abdominal mass discovered by parents during bathing or by a doctor during a routine exam. The mass is usually smooth, firm and rarely crosses the midline. Individuals who are symptomatic may present with abdominal pain, fever, anemia, hematuria, and hypertension. The tumor may compress on the renal artery causing renal ischemia leading to renin secretion with resulting hypertension (2). Post-streptococcal glomerulonephritis may be mistakenly diagnosed in cases presenting with hematuria and hypertension. Individuals may also present with abnormalities that may link them with the syndromes associated with Wilms' tumor (WAGR, Denys-Drash, Beckwith-Wiedemann). Rarely, a paraneoplastic syndrome may arise in which erythropoietin is released causing polycythemia (15).

An abdominal mass is linked with a variety of diseases all of which needs to be included in the differential. Those that are of importance include neuroblastoma, rhabdomyosarcoma, leiomyosarcoma, renal cell sarcoma, fibrosarcoma, hydronephrosis, polycystic kidney, adrenal hemorrhage, and renal vein thrombosis (13).

Imaging studies (ultrasound or CT) are required to confirm the presence of a renal mass. Once a Wilms' tumor is suspected, a complete blood count, liver and kidney function tests, skeletal survey, and chest x-ray should also be done. Ultrasound or CT helps localize the mass, identifies associated genitourinary abnormalities, confirms function of the contralateral kidney, and indicates if there is extension to the inferior vena cava (16). CT scan is better at detecting subtle intra-abdominal abnormalities such as tumor spread, lymph node enlargement, vascularity, etc. Chest x-rays are done to look for evidence of lung metastasis. A definitive diagnosis is made based on biopsy results (13).

The National Wilms' Tumor Study Group Staging System is the most common criteria used to stage a tumor. This system stages tumors according to information gathered by clinicians, surgeons, and pathologists.

The first line of treatment is surgical resection whenever possible. During the procedure the surgeon should remove the tumor taking precautions to prevent tumor spillage. While the abdomen is open, the contralateral kidney should be inspected to detect involvement. The liver should also be inspected for evidence of metastasis. The renal vein should be checked to see if the tumor has extended to this area. Lastly, a retroperitoneal lymph node sample should be obtained for histopathology. If the tumor is inoperable either due to large size or the presence of invasion, a biopsy should be taken and other forms of therapy started (15). This tumor is sensitive to chemotherapy and radiation so either of these treatment options are possible therapeutic choices.

If there is bilateral Wilms' tumor, complete resection is not an option since dialysis or a renal transplant would be required to prevent uremia. Instead, renal sparing surgery is preferred. First, a biopsy must be done to confirm bilateral involvement and to get histologic data to grade the tumors. Next, preoperative chemotherapy, appropriate for the stage of the tumor, is begun which lasts for up to six weeks. An abdominal CT scan is then done to determine if resection is possible. If it looks good, surgical excision is done. If it does not appear to be resectable, a second-look procedure is done in which another biopsy is taken and a partial resection is attempted. If a partial resection is not possible, then chemotherapy is utilized with or without radiation (16).

The prognosis of the patient is based on the histology (grade) and stage of the tumor. A favorable histology is one in which blastemal, stromal, and epithelial elements may be seen. An unfavorable histology is an anaplastic one detectable by the presence of gigantic polypoid nuclei within the tumor sample (14). Four year Wilms' tumor survival (4): Stage I with favorable histology (96%), stage II with favorable histology (92%), stage III with favorable histology (87%), stage IV with favorable histology (83%), unfavorable histology (60%).

Questions

1. A 2 year old boy presents with a large right flank mass, fever, weight loss, proptosis of the right eye, and ecchymosis around the right eye. The most likely diagnosis is:
   a. Wilms' tumor
   b. Neuroblastoma
   c. Hydronephrosis
   d. Metastatic neuroblastoma

2. What is the most common secondary tumor that develops after survival of retinoblastoma?
   a. Neuroblastoma
   b. Soft tissue sarcoma
   c. Osteosarcoma
   d. Acute lymphocytic leukemia

3. Which one of the syndromes in the following list is not associated with Wilms' tumor?
   a. Beckwith-Wiedemann syndrome
   b. Li-Fraumeni syndrome
   c. WAGR syndrome
   d. Denys-Drash syndrome

4. If a teenager comes in complaining of night pain in his knee, which disorder should be at the top of your differential? Which would be the most likely, and which would be the most serious likely consideration?
   a. Juvenile Rheumatoid Arthritis
   b. Osteosarcoma
   c. Paget's Disease
   d. Stress fracture
   e. Growing pains

5. Retinoblastoma is often detected by:
   a. Primary care physicians performing routine ophthalmoscopy checks for a red reflex, but finding a white reflex instead.
   b. Flash photography of infants and children done by family members.
   c. Incidental finding on CT scans done for head trauma.
   d. Genetic counseling and risk analysis.
   e. Detection of an orbital bruit.

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Answers to questions

1. d
2. c
3. b
4. Growing pains (e) are ill-defined, but are supposedly very common, so from a numerical standpoint, this diagnosis is probably the most common. However, since this age group is one of the peak ages for osteosarcoma (b) and since this is a serious condition that should be diagnosed as early as possible, osteosarcoma is the most serious likely consideration.
5. a, b, and d are correct.

Chapter XII.4. Palliative Care

Dianne Fochtman, RN, MN, CPNP, CPON

A 10 year old boy presents to the pediatric oncology ward with epistaxis for 2 hours and hematemesis. He complains of nausea, constipation, severe hip pain and headache. He has a history of recurrent Stage IV neuroblastoma, initially diagnosed 2 years ago, treated with chemotherapy and a bone marrow transplant. He received chemotherapy again when his cancer recurred six months ago. Initially his tumor responded, but eventually it progressed and includes bone marrow involvement. He has started experimental chemotherapy at the request of his parents, with his assent. He has multiple metastatic bone lesions, most pronounced on his head and right hip. He has required increasing doses of pain medications. He has been attending school a few hours a day, but this week he has been increasingly tired with increased pallor. This morning, he woke up with epistaxis that would not stop with pressure. About 1 hour later he started vomiting bright red blood. He is currently taking 8 mg of hydromorphone (Dilaudid) orally every 6 hours around the clock for pain. He rates his current pain level as a 6 on a scale of 10.

Exam: VS T 37, P 120, RR 18, BP 100/50. His skin is pale and dry with multiple bruises. He has multiple lumps on his scalp. Dried blood, blood clots and some oozing blood is noted in both nares. Subconjunctival hemorrhages and pallor are noted. His neck is supple with no lymphadenopathy. Heart regular rate without murmurs. Lungs are clear. A central venous catheter is present in his left anterior chest. His abdomen is soft with no hepatosplenomegaly. There is mild tenderness. Exam of his extremities is significant for bruising and pallor. He has moderate tenderness over his back, hips and pelvis.

Lab: WBC 2.4, 70% neutrophils, Hgb 6.2, Hct 19.6, platelet count 3,000.

Hospital Course: He receives packed RBC transfusions to correct his anemia (which may also improve his stamina) and platelet transfusions which stop his epistaxis. He is started on MS Contin (slow release morphine) 60 mg PO q12 hrs with morphine 15 mg PO for breakthrough pain as needed which controls his pain well. His physician discusses the future use of IV morphine on a patient controlled analgesia (PCA) pump. He is started on Senokot (senna) to prevent constipation. Since he seems to improve, or at least remain stable, with the experimental chemotherapy, this is continued.

Palliative care is a broad philosophy of total compassionate care for children when their disease no longer responds to curative treatment. The goal is to give the best quality of life by preventing and relieving suffering. Palliative care affirms life and recognizes death as a normal process. It does not hasten death, nor does it postpone it. The objectives are to prevent or relieve physical symptoms, maintain activity and independence for as long as comfortably possible, alleviate psychological distress, and support those who are bereaved.

Interventions are defined as "palliative" by their therapeutic intent (e.g., comfort) rather than the type of intervention (e.g., radiation, medication, surgery). So that unrealistic expectations are not encouraged, parents and staff must be clear that the purpose is to make the child more comfortable, not to cure the child. Many of the interventions in palliative care focus on symptom management.

To minimize fatigue, prioritize the child's activities, prevent sleep disruptions, and provide rest periods. If they are anemic, consider transfusion depending on their potential for improved quality of life.

For respiratory difficulty, an early objective should be to improve their respiratory effort, and later focus on alleviating anxiety due to respiratory changes and shortness of breath. Other measures include: 1) oral-pharyngeal suctioning as needed, 2) opioids for dyspnea or cough, 3) cough suppressants (dextromethorphan) for dry, nonproductive cough and expectorants (guaifenesin) for wet, productive cough secondary to infection, 4) supplemental oxygen may be needed, 5) anticholinergic medications for increased secretions or dyspnea related to congestion, 6) bronchodilators for dyspnea, wheezing or congestion, 7) diuretics for pulmonary edema, 8) anxiolytic medications for dyspnea with anxiety, 9) aerosolized morphine for dyspnea. A pleural effusion or pneumothorax may require invasive procedures to increase comfort, but this must be weighed against the discomfort of the procedure

For anorexia, treat the contributing factors (nausea, vomiting, pain, constipation). Consider medications to increase appetite, such as prednisone, Marinol (dronabinol) or Megace (megestrol). Benefits to quality of life must be weighed when considering aggressive nutritional support (TPN, enteral feedings).

Nausea and vomiting can be reduced by using antiemetics such as Zofran (ondansetron), Kytril (granisetron) or Anzemet (dolasetron). Consider changing the opioid medication to one which causes less nausea.

Start a laxative regimen to prevent constipation if opioid therapy is used. Treat constipation promptly when it occurs. Mineral oil eases passage of stool by decreasing water absorption, softens stool and lubricates the intestines. If no fecal impaction or bowel obstruction exist, use stimulant laxatives such as Senokot (senna). Avoid suppositories in neutropenic or thrombocytopenic patient. Add fruits, vegetables, and fiber to the diet, and encourage fluids and activity.

For diarrhea, stop all laxatives, avoid milk products, fats and protein. Anti-diarrheal medications such as Imodium (loperamide) and oral electrolyte solutions can be administered if tolerated.

For febrile patients, administer antibiotics for infection, and antipyretics such as acetaminophen, ibuprofen, other NSAIDS or indomethacin (use with caution if the patient is thrombocytopenic).

For insomnia, maintain normal sleeping and waking routines and discourage daytime naps if they are awake at night. Sedative/hypnotics such as Ativan (lorazepam) can be given as needed (watch for interaction with pain medications), but are seldom necessary in the pediatric oncology patient. Avoid corticosteroids at bedtime because of the stimulating effect. Initiate interventions to deal with fears, dreams or nightmares.

Pain control is often the greatest challenge in palliative care. Medication should be used as needed in adequate doses on an appropriate schedule to relieve the pain. Multiple agents are available, ranging from acetaminophen to opiates, which can be given by several different routes. A major challenge is to give sufficient medication to relieve the pain while maintaining as much alertness as the child and family wish. Concerns must be allayed about addiction and the amount of medication sometimes required to eliminate the pain. The amount of medication required is whatever it takes to eliminate the pain.

For optimal pain control, administer pain medications around the clock rather than on an as needed basis. Choose the least traumatic and simplest route of administration. Include co-analgesic medications (acetaminophen, antidepressants, anticonvulsants, NSAIDS) as needed. Establish an alternative plan to be used if the pain increases or if oral medications become less effective. With the start of opiate analgesics, initiate measures to prevent constipation (a common side effect). Use non-pharmacologic pain reduction measures (massage, distraction, music, relaxation) when appropriate

The decision to stop monitoring labs and to stop transfusing blood products when blood counts are low is a difficult one. Routine blood testing is usually not performed in palliative care and the use of transfusions is based on clinical symptoms. Treatment of bleeding is directly related to the child's comfort and the degree of unpleasantness witnessed by the family. Increased bruising and petechiae do not produce discomfort, but severely bleeding gums, uncontrolled epistaxis, or severe GI bleeding can cause discomfort and increase anxiety. Red blood cell transfusions may be given if the child is very tired from anemia and wants to remain active, or has headaches related to anemia, but anemia is not painful and transfusions may not improve the child's activity level. There may come a time when transfusions prolong the dying process and not the living.

Questions

1. True/False: There is no "ceiling" on the amount of pain medication that can be used in palliative care.
2. True/False: Transfusions are not appropriate for terminally ill patients.
3. True/False: NSAIDS and acetaminophen can potentiate the action of opioids
4. True/False: The amount of pain medication required is whatever it takes to eliminate the pain.
5. True/False: Although the physical suffering related to a child's dying may not be totally eliminated, there is no reason for the child to be in pain.

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Answers to questions

1.True, 2.False, 3.True, 4.True, 5.True

Chapter XIII.1. Nephritic Syndrome
Teresa M. Bane-Terakubo, MD

A 7 year old male presents to his primary care physician with the chief complaint of dark "cola colored" urine, facial puffiness and abdominal pain for the past 2 days. He had been in his usual state of good health until 14 days ago when he had a sore throat and fever. His sore throat and fever resolved. He was not seen by a physician at that time. Over the past 2 days facial puffiness has been noted, but no swelling of his hands or feet. He has had some nonspecific abdominal pain that comes and goes which does not seem to be related to eating or bowel movements. There is no nausea or vomiting. His urine is dark brown and he has not been voiding as much as usual, only 2 times in the past 24 hrs. There is no urinary frequency, urgency, dysuria or foul smell to the urine. His appetite has been poor although he is still drinking fluids well. He is also complaining of some back pain in the flank area that he describes as a dull pain that comes and goes and does not seem to be related to activity. His energy level is down and he has not felt up to going to school for the past 2 days. He is also complaining of a dull generalized headache that has not been relieved with acetaminophen.

Review of systems is negative for recent skin infection, skin rash, cough, rhinorrhea, seizure activity, fever, arthralgia or weight loss. His past medical history, family history and social history are unremarkable.

Exam: VS T 37, P 100, RR 20, BP 120/75, oxygen saturation 100% in RA. Height and weight at 50th %tile. He is tired appearing but in no acute distress. Pupils are equal and reactive. Optic disc margins are sharp. Sclera are white and conjunctiva are clear. Mild periorbital is edema noted. TMs are normal. Throat, oral mucosa and nose are normal. His neck is supple without lymphadenopathy. Heart is regular without murmurs. Lungs are clear. Abdomen is diffusely tender (mild), without guarding or rebound. Bowel sounds are normal. No organomegaly is noted. Mild CVA tenderness is present. His extremities are warm, with strong pulses. Capillary refill is less than 2 seconds. No edema is noted in his legs, feet or hands. No skin rashes or impetigo scars are noted. His genitalia are normal. No scrotal edema is present. Neurologic exam is normal.

Lab: His urine is tea colored. UA shows an increased specific gravity. A dipstick is positive for a large amount of blood and moderate protein. RBCs are too numerous to count. 5-10 WBCs per HPF. RBC casts are present. CBC with diff is normal. Throat swab is sent for culture. ASO titer is elevated. Serum complement C3 level is low. Serum electrolytes are normal. BUN 23 and Cr 0.8.

Clinical Course: He is diagnosed with acute poststreptococcal glomerulonephritis. He is initially hospitalized for treatment of oliguria/volume overload with furosemide, and monitoring of his modest hypertension. He has a good urine output with the furosemide, however he later requires a calcium channel blocker to control worsening hypertension. He is placed on a fluid and sodium restricted diet. His throat culture later returns positive for group A beta hemolytic streptococci (GABHS), so he is given a course of penicillin. He is discharged after 3 days of hospitalization. His hypertension resolves over the next 2 weeks. He is followed closely by his primary physician and his proteinuria and gross hematuria resolve early. His C3 level normalizes two months after the onset of illness. Microscopic hematuria is expected to persist for months so this will be rechecked in 3 to 6 months. He does not develop any long term complications.

Acute glomerulonephritis (GN) presents with hematuria, oliguria, hypertension and volume overload (edema), which are the findings of the classic "nephritic syndrome". Acute GN (AGN) is associated with inflammation and proliferation of the glomerular tuft. Most AGN is immunologically mediated. In acute poststreptococcal glomerulonephritis (APSGN), immune complexes form with streptococcal antigens, localize on the glomerular wall, activate the complement system, and initiate a proliferative and inflammatory response. AGN may be rapidly progressive (RPGN). Chronic GN (CGN) implies that permanent damage has occurred.

Acute poststreptococcal glomerulonephritis (APSGN) is the most common form of glomerulonephritis in children. APSGN can occur in all ages but is most frequent in males between 5 and 15 years. APSGN can occur after either an upper respiratory tract or skin infection due to GABHS. It is more common after an infection of the throat. CGN occurs more often in teenagers and adults. There are genetic predispositions for familial GN (Alport, X-linked) and autoimmune etiologies (e.g., SLE-lupus nephritis). Goodpasture's disease (anti-basement membrane autoantibodies) also presents with a classic nephritic syndrome in conjunction with hemoptysis, but this condition is rare.

Important questions to ask the patient/caregiver include history of macroscopic (gross) hematuria (tea or cola colored urine, or red colored urine), sore throat, impetigo, prior URI at least 1 week previously or skin sores (impetigo) in the preceding 3-4 weeks (suggestive of APSGN), URI in the preceding few days (suggestive of IgA nephropathy), reduced urine output, dyspnea, fatigue, lethargy, headache or seizures (hypertensive encephalopathy). Also, symptoms of a systemic disease such as fever, vasculitic rash (especially on the buttocks and legs posteriorly), arthralgia and weight loss may be present. On physical exam, pay particular attention to hypertension, pallor, signs of volume overload (edema, jugular venous distention, hepatomegaly, crackles in the lung bases), impetigo and rash. For PSGN, edema (specifically, facial edema involving the periorbital area) is the most frequent presenting symptom. Dark colored or bloody urine is frequently not noticed by patients because the abnormal color is only visible when the urine is collected in a cup. The abnormal color is not noticeable in a urine stream unless the urine color is very dark.

Many patients with APSGN are asymptomatic and do not seek medical care. Mild hypertension is often asymptomatic. The classic dark urine is often not noticed. Screening urinalysis may often identify persistent microhematuria which eventually resolves months later. Many of these cases are felt to be resolving APSGN cases which never presented for medical attention during the acute nephritis phase.

Throat culture for GABHS will be positive in 15-20% of patients with APSGN. CBC is normal in AGN and with chronic renal insufficiency a normocytic normochromic or hypochromic microcytic anemia will usually be found. Serum chemistries will reflect the degree of renal failure (BUN, creatinine, potassium and phosphate are all elevated, while calcium is decreased), which is usually mild. The ASO titer will be positive in 60% of patients with APSGN. The complement C3 serum level will be low in APSGN and in other causes of GN described below. Urine microscopy shows RBC casts and crenated RBCs in AGN. EKG, CXR and renal ultrasound are other tests that should be considered. RBC casts indicate the presence of acute nephritis. WBC casts can also be seen in APSGN, interstitial nephritis and pyelonephritis.

During convalescence from APSGN, complement C3 levels return to normal within 6-8 weeks. Persistently low C3 levels indicate an etiology other than APSGN. Gross hematuria will generally resolve within 1 to 2 weeks. Microscopic hematuria may persist for a year or more.

The differential diagnosis for glomerulonephritis includes infectious etiologies such as GABHS, pneumococcus, mycoplasma, mumps and EBV. Glomerulonephritis may also be related to hepatitis B and C as well as syphilis infections. IgA nephropathy, membranoproliferative GN, autoimmune GN, familial GN, acute interstitial nephritis, hemolytic uremic syndrome and pyelonephritis

should all be on your differential diagnosis list. One way to sort out the etiology of the glomerulonephritis is to look at the complement level and whether evidence of systemic or renal disease is present. For a patient with low serum complement level and systemic disease consider vasculitis and autoimmune disease (SLE), subacute bacterial endocarditis, shunt nephritis and cryoglobulinemia. For a patient with low serum complement level and evidence of renal disease consider APSGN and membranoproliferative glomerulonephritis (types 1,2, and 3). In a patient with normal serum complement level and evidence of systemic disease consider polyarteritis nodosum, Wegener vasculitis, Henoch-Schonlein purpura and hypersensitivity vasculitis. In a patient with normal serum complement and evidence of renal disease consider IgA nephropathy, idiopathic RPGN and immune complex disease. A renal tumor (e.g., Wilms) will occasionally present with gross hematuria so an imaging study may be indicated to rule this out.

APSGN is a self-limiting disease. Treatment is symptomatic. Restricted fluid and sodium diets are initially beneficial. Potassium and phosphate may also need to be restricted. Medication may be required for management. Loop diuretics (e.g., furosemide) are the first choice for volume overload, hypertension and hyperkalemia control. Vasodilators such as calcium channel blockers are also used to manage hypertension. IV antihypertensives may also be required to treat severe refractory hypertension. In severe hyperkalemia serum potassium lowering agents and IV calcium may be needed. Immunosuppressive agents are used in the treatment of vasculitis associated GN, membranoproliferative GN and RPGN. Plasmapheresis may be used to treat RPGN.

Most patients with APSGN do not need hospitalization. Indications for hospitalization include: an uncertain diagnosis, significant hypertension, anticipated poor follow-up, cardiovascular or cerebrovascular compromise, etc. The diagnosis can usually be firmly established as an outpatient. An imaging study may be necessary to rule out a Wilms tumor. If the patient's blood pressure is normal or only mildly elevated, most parents can be taught to measure the child's blood pressure at home using an automated blood pressure measurement device which is easily available at most stores. Parents must notify the physician when the blood pressure exceeds the parameters given by the physician. If the parents are deemed to be unreliable, or are not capable of measuring the child's blood pressure, then hospitalization should be considered.

Prognosis is excellent for APSGN and variable for other causes of GN in children. Complications of AGN include acute renal failure, hyperkalemia, hypertension, volume overload (congestive heart failure, pulmonary edema, hypertension) and chronic renal failure.

Questions

1. When does the complement C3 level return to normal in APSGN?
2. What is the significance of finding red cell casts in the urine?
3. What is the significance of finding white cell casts in the urine?
4. How long does hematuria persist in APSGN?
5. Describe some indications for hospitalization of patients with APSGN.
6. What are the clinical elements of the nephritic syndrome?
7. What are classic causes of the nephritic syndrome?
8. A 5 year old boy has a screening urinalysis as part of a general physical exam. The UA shows microscopic hematuria. History suggests that he has impetigo periodically. What a likely cause for the microscopic hematuria?

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Answers to questions

1. C3 levels return to normal within a 6-8 week period in APSGN. Persistently low C3 levels suggest a cause other than APSGN.
2. The presence of red cell casts on urinalysis almost always indicates the presence of glomerulonephritis. They can also be seen after strenuous exercise and renal trauma.
3. The presence of white cell casts on urinalysis can be seen in APSGN, interstitial nephritis and pyelonephritis.
4. Gross hematuria resolves within days to weeks. Microhematuria may persist for months.
5. An uncertain diagnosis, significant hypertension, anticipated poor follow-up, cardiovascular or cerebrovascular compromise, etc.
6. Gross hematuria, oliguria, hypertension, edema (usually mild).
7. APSGN and Goodpasture’s. Other causes of nephritis include SLE nephritis, MPGN, RPGN, Alport's, etc.
8. Convalescing APSGN.

Chapter XIII.2. Nephrotic Syndrome
Paul J. Eakin, MD

A previously well 5 year old male presents to your office with the chief complaint of facial puffiness. His mother noticed this a few days ago and it seems to be worsening. He has no other symptoms, but about two weeks ago had "a bad cold."

Exam: VS T 37, HR 90, RR 20, BP 92/55. He is alert and cooperative with the examination. His face shows moderate periorbital edema. His eyes are non-injected, his conjunctiva are not edematous and his throat is not red. His heart is regular without murmurs. Heart sounds are normal. His lung exam shows good aeration, with no crackles or rhonchi. Abdomen is soft, non-tender, non-distended and without masses or shifting dullness. No hepatosplenomegaly. He has normal male genitalia with no scrotal edema. The dorsal surfaces of his hands and feet have mild pitting edema. He has brisk capillary refill and 2+ pulses. No rashes are noted.

Urinalysis shows 4+ protein, and a specific gravity of 1.030. His chemistry panel is remarkable for protein of 2 g/dL, serum albumin of 1.4 g/dL and cholesterol of 350 mg/dL. BUN and creatinine are normal.

He is not ill enough to require hospitalization. He is started on oral prednisone BID. He is followed as an outpatient clinically and by daily urine dipsticks. His edema and proteinuria gradually resolve with treatment. His corticosteroids are tapered off and he remains stable.

Nephrotic syndrome describes the collection of clinical and laboratory findings secondary to glomerular dysfunction, resulting in proteinuria. The diagnostic criteria are marked proteinuria, generalized edema, hypoalbuminemia, and hyperlipidemia (with hypercholesterolemia). The proteinuria in nephrotic syndrome is severe, exceeding 50 mg of excreted protein for every kilogram of body weight over 24 hours. Primary nephrotic syndrome refers to diseases limited to the kidney, whereas secondary nephrotic syndrome indicates systemic diseases that include kidney involvement (e.g., diabetic nephropathy).

In healthy children (less than 18 years of age), the annual incidence of nephrotic syndrome is 2-7 new cases per 100,000. The prevalence is approximately 16 cases per 100,000 children, making nephrotic syndrome one of the most frequent reasons for referral to a pediatric nephrologist. Also, the most common type of nephrotic syndrome is recurrent to some degree, so cases will often manifest repeatedly over time. The peak age for the onset of nephrotic syndrome is 2-3 years of age. In early childhood, males outnumber females about 2:1 for new cases of nephrotic syndrome. In adolescence and adults, the gender distribution is more equal. Primary nephrotic syndrome is more common in children less than six years of age, while secondary nephrotic syndrome predominates for patients older than six. The disease inheritance is usually sporadic, although there is a congenital form of nephrotic syndrome, called Finnish type congenital nephrosis, which is inherited in an autosomal recessive manner. This abnormality has been mapped to a defect in the nephrin gene on chromosome 19q13.1 that codes for a protein in the glomerular basement membrane.

The main pathogenic abnormality in nephrotic syndrome is an increase in glomerular capillary wall permeability, resulting in pronounced proteinuria. The normal glomerular wall is remarkably selective for retaining protein in the serum. Once this selectivity is lost, the excretion of large amounts of protein will follow. This increase in permeability is related to the loss of negatively charged glycoproteins within the capillary wall that usually repel negatively charged proteins. The predominant protein lost is albumin, although immunoglobulins are also excreted. The pathophysiology for the formation of edema is incompletely understood. A simplification of the predominant theory is that after the plasma albumin concentration drops, secondary to protein excretion, the plasma oncotic pressure drops. With the decrease in oncotic pressure, fluid moves from the intravascular space to the interstitial space causing edema. The liver has a very large capacity to synthesize protein, so the persistent hypoalbuminemia is likely not due entirely to increased losses. Reduction of the intravascular volume results in activation of the renin-angiotensin-aldosterone system. Sodium and water are retained, which further increases the edema. There are likely other factors involved in the formation of edema, because some patients with nephrotic syndrome have normal or increased intravascular volume.

The hyperlipidemia in nephrotic syndrome is characterized by elevated triglycerides and cholesterol and is possibly secondary to two factors. The hypoproteinemia is thought to stimulate protein synthesis in the liver, including the overproduction of lipoproteins. Also lipid catabolism is decreased due to lower levels of lipoprotein lipase, the main enzyme involved in lipoprotein breakdown.

More than 90% of children with primary nephrotic syndrome have idiopathic nephrotic syndrome and this will be the focus of this chapter. The etiology of this condition remains largely unknown, but some have postulated an immunologic mechanism. Supporting evidence for this theory include the characteristic response to corticosteroids and cytotoxic agents, an observed increased incidence of concurrent allergic conditions, and spontaneous remissions with natural measles infections (known to induce suppression of cell-mediated immunity). Evidence against an immunologic etiology is a failure to identify immune reactants or inflammation in kidney biopsies.

There are three morphological patterns of idiopathic nephrotic syndrome, with minimal change disease (also called "nil disease") making up 80-85% of the cases. In this condition, the glomeruli appear normal or have a minimal increase in the mesangial cells or matrix. As well as being the most common form of primary nephrotic syndrome, minimal change disease also has the mildest clinical course. The rest of this chapter will focus on this disease entity after briefly describing the other forms of primary nephrotic syndrome as well as secondary nephrotic syndrome. The less commonly seen types of primary idiopathic nephrotic syndrome are focal segmental glomerular sclerosis, membranous glomerulonephritis and membranoproliferative glomerulonephritis.

Focal segmental glomerular sclerosis is found in about 7-15% of patients with nephrotic syndrome, making it the second most common primary renal lesion. It tends to have a more severe clinical course with persistent proteinuria, progressive decline in glomerular filtration rate and hypertension that can be unresponsive to therapy. Renal failure occurs, with dialysis or transplant being the only treatment options. Unfortunately, the recurrence rate of focal segmental glomerular sclerosis can be as high as 40% after renal transplant.

Membranoproliferative glomerulonephritis accounts for roughly 7% of primary idiopathic nephrotic syndrome. These patients often have hematuria, hypertension and mild azotemia. Another characteristic finding is persistently depressed C3 levels. The clinical course is variable with only a small percentage of patients going into remission.

Membranous glomerulopathy is rare in the pediatric age group, but becomes more common into adolescence and adulthood. It is often associated with infections, with hepatitis B being the most common. The clinical course is variable, but the overall prognosis is good, with spontaneous remission of proteinuria occurring in 50-60% of cases.

There are many different causes of secondary nephrotic syndrome in children. These include multisystemic diseases such as systemic lupus erythematosus and Henoch-Schonlein purpura, malignancies such as Hodgkin disease or leukemia, drug or toxin exposures such as mercury, gold, penicillamine or bee sting, and infectious etiologies such as Epstein-Barr virus, cytomegalovirus and tuberculosis.

Children with idiopathic nephrotic syndrome secondary to minimal change disease usually present with edema. Clinically apparent edema usually is not seen until albumin levels drop below 2 g/dL. The edema is initially noted around the eyes and in the lower extremities. Over the course of a day, the edema often distributes from the eyes to more dependent areas. After time, the edema becomes more pronounced, generalizes and there can be weight gain. Patients or parents may notice tighter fit of clothes, belts and shoes and scrotal or labial edema often occurs. As the edema accumulates, pleural effusions, ascites and decreased urine output may develop. In many cases, there is a history of preceding upper respiratory symptoms. Anorexia, abdominal pain and diarrhea may be seen, possibly secondary to the formation of ascites. Blood pressure and renal function are usually normal.

The hallmark of nephrotic syndrome is severe proteinuria, most reliably diagnosed using a 24-hour urine collection. Spot urinalysis is also informative and reveals +3 to +4 proteinuria (300 to 1000 mg/dL), with a specific gravity usually greater than 1.020. Gross hematuria is not common. Blood samples show decreased albumin levels usually less than 2.0 mg/dL and elevated triglyceride and cholesterol levels. Because of the hypoalbuminemia, hypocalcemia is often seen, with calcium levels less than 9.0 mg/dL. Usually the ionized calcium will be normal. Hyponatremia and hyperkalemia can be seen, with hyperkalemia developing in patients who are oliguric. Serum C3 levels are normal in cases of minimal change disease.

Renal biopsy is not necessary for the child with newly diagnosed nephrotic syndrome and the initial treatment will be the same, regardless of the cause. How the disease responds to corticosteroids may help dictate the need for biopsy. If the response is good and renal function is normal, the diagnosis of minimal change disease may be presumed. If relapses respond to corticosteroids and there is no proteinuria during disease free periods, this diagnosis is strengthened. Biopsy is generally obtained in cases where there is poor or no response to corticosteroids, the patient is less than 1 year old (high likelihood of congenital nephrotic syndrome) or over 10 years old, secondary nephrotic syndrome is suspected, there is corticosteroid toxicity, or the use of a cytotoxic agent is being considered. Patients with low serum complement levels or hypertension on presentation may require biopsy since these conditions are not characteristic of minimal change disease and may indicate other renal lesions.

The treatment of primary idiopathic nephrotic syndrome of childhood is corticosteroid therapy and supportive care. Steroid therapy will be discussed below. Many patients may be treated on an outpatient basis, although the newly diagnosed patient is sometimes admitted for diagnostic and educational purposes. Edema is managed with sodium restriction (the "no added salt diet") and diuretics such as hydrochlorothiazide. If hypokalemia develops, an oral potassium supplement or spironolactone may be added. Aggressive use of loop diuretics may be harmful since most patients initially presenting with nephrosis are hypovolemic. The use of diuretics necessitates close monitoring of patients. Patients need to monitor their weight closely and consume adequate amounts of protein.

Conditions that require immediate attention and hospitalization are severe scrotal edema, dehydration (more than 10% dehydrated), respiratory compromise due to pulmonary edema or pleural effusions, and peritonitis or suspected bacterial infection. Despite their edematous appearance, most patients have decreased intravascular volumes. Therapy is aimed at the restoration of intravascular volume and preventing volume overload. Intravenous fluids are used, sometimes with the infusion of albumin to increase the serum oncotic pressure. The albumin must be given slowly, over 8-12 hours, to prevent fluid overload from rapid intravascular volume expansion. There is some debate over the use of albumin, since the effect seems to be transient and it is presumably excreted rapidly (1). Electrolyte levels and renal function must be closely monitored. Once the intravascular volume is restored, diuretic therapy is used to mobilize the fluid and prevent volume overload. Paracentesis is performed if there is respiratory compromise secondary to severe ascites. Antibiotic therapy to cover for the most common pathogens should be started if there is evidence of bacterial infection (discussed below).

Minimal change disease is characteristically responsive to corticosteroid therapy and once the diagnosis is confirmed with laboratory testing, steroid therapy should be started. Prednisone is initiated with a dose of 60 mg/sq-meter/day or 2 mg/kg/day divided in 2-3 doses. The daily dose is continued until the proteinuria resolves, usually in 2-3 weeks. Some sources suggest continuing the daily dose for 4-6 weeks (1). Regardless, the corticosteroids are continued and then tapered over the course of 3-6 months. In patients with minimal change nephrotic syndrome, approximately 98% will eventually have satisfactory therapeutic responses. This disease is one of frequent relapse, with two thirds of patients having a single relapse and roughly one third experiencing repeated relapses over many years. Most patients with steroid-responsive nephrotic syndrome will continue to have relapses until they are in their late teens. Relapses are treated the same as the initial presentation. With repeated relapses or severe steroid toxicity (growth retardation, elevated blood pressure), cytotoxic agents such as cyclophosphamide are added to a lower corticosteroid dose. This agent has been shown to prevent relapses and to increase the duration of remission. Chlorambucil and less commonly cyclosporine have also been used for remission induction. Another regimen for patients refractory to corticosteroids is indomethacin and an angiotensin-converting enzyme (ACE) inhibitor.

The most common complications of nephrotic syndrome are bacterial infection and thromboembolism. There are also complications secondary to medications such as the gastric irritation and insulin resistance seen with corticosteroids or the hemorrhagic cystitis, sterility and leukopenia seen with cyclophosphamide. The tendency to develop infections, especially "primary peritonitis" (a type of pneumococcal sepsis), is thought to be due to IgG excretion, decreased complement function, and diminished splanchnic blood flow. The organisms causing peritonitis are most commonly Streptococcus pneumoniae and Escherichia coli. Peritonitis should always be considered in a patient who has nephrotic syndrome and abdominal pain or fever. Antibiotics such as ampicillin or vancomycin with a third generation cephalosporin or an aminoglycoside would provide good empiric coverage. Other infections such as sepsis, cellulitis, pneumonia and urinary tract infection are also seen. The signs of infection may be masked if the patient is currently on corticosteroid therapy. Any child with nephrotic syndrome and a fever must be thought of as having an infection until proven otherwise, since they are at high risk for sepsis, similar to splenectomy patients. Because of their predilection for S. pneumoniae infection, polyvalent pneumococcal vaccine should be administered to children over two years of age.

Another complication, thromboembolism is thought to be more common secondary to increased platelet aggregation, increased fibrinogen concentration, decreased antithrombin III concentrations, increased blood viscosity and decreased blood flow. Venous thrombosis is most common, especially in the renal vein, pulmonary artery, and deep vessels of the extremities. In patients with refractory nephrosis, low dose anticoagulants are sometimes used.

The prognosis for children with minimal change nephrotic syndrome is good, with most patients ultimately becoming disease free and living a normal life. Mortality is approximately 2% with the majority of deaths being secondary to complications such as peritonitis or thromboembolic disease.

Questions

1. The most common cause of primary idiopathic nephrotic syndrome is:
    a. Focal segmental glomerular sclerosis
    b. Membranoproliferative glomerulonephritis
    c. Membranous glomerulopathy
    d. Minimal change disease

2. Common causes of mortality in primary nephrotic syndrome is/are:
    a. Acute renal failure
    b. Thromboembolism
    c. Congestive heart failure
    d. Peritonitis
    e. Seizure

3. True/False: A renal biopsy is necessary to confirm the diagnosis of primary idiopathic nephrotic syndrome.

4. The inheritance pattern of primary idiopathic nephrotic syndrome is/are:
    a. Autosomal recessive
    b. X-linked recessive
    c. Autosomal dominant
    d. Sporadic

5. Reasons for biopsy in a patient with nephrotic syndrome include:
    a. Continued proteinuria after a week of prednisone therapy.
    b. Age at onset of 10 months.
    c. Relapse 1 year after initial course of therapy.
    d. Cholesterol level greater than 400 mg/dL.
    e. A patient who has a history of systemic lupus erythematosus

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Answers to questions

1. d. Minimal change disease or "nil disease" accounts for 80-85% of cases of primary idiopathic nephrotic syndrome in childhood.
2. b and d. Infection, especially peritonitis and thrombosis account for the majority to nephrotic syndrome mortality.
3. false. The decision to perform a renal biopsy is usually deferred until the initial course of corticosteroid is initiated, unless there are specific risk factors such as age below one or above 10, hypertension on presentation or decreased complement on presentation.
4. d. Primary nephrotic syndrome is sporadic in nature. Congenital nephrotic syndrome is passed in an autosomal recessive manner.
5. b and e. Nephrotic syndrome in a child less than 1 year old may indicate congenital nephrotic syndrome and renal biopsy is often performed. In a patient with SLE, the nephrotic syndrome is likely secondary and a renal biopsy is indicated.

Chapter XIII.3. Cystic Kidneys
Miki E. Shirakawa

A one month old female is brought to her pediatrician with a chief complaint of an abdominal mass. Her mother noticed the mass earlier in the week and immediately made an appointment to see the pediatrician. The mother also notes that the infant has been frequently wetting her diapers, although there is no history of fever, vomiting or diarrhea. The infant's perinatal and birth history are unremarkable (spontaneous vaginal delivery at term with a birth weight of 2750 grams). There is a family history of cystic kidneys in the infant's 14 year old brother. The infant's four other brothers and sisters do not have any renal disease and both parents do not have a history of renal disease.

Exam: VS T 37.5, P 110, R 26, BP 115/85, Weight 3.32 kg (10th percentile). She is alert and active, in no distress. Her physical exam is unremarkable except for a nontender 7 cm by 8 cm left-sided abdominal mass.

Urinalysis reveals cloudy urine, positive for leukocyte esterase and nitrites. A renal ultrasound is ordered and reveals bilateral enlargement of her kidneys with diffuse echogenicity and microcysts. A hepatic ultrasound reveals periportal fibrosis. The infant is diagnosed with autosomal-recessive polycystic kidney disease and a possible urinary tract infection. She is hospitalized for antibiotic treatment and further evaluation. She improves and is discharged from the hospital. Her renal function is sufficient, but it is anticipated that it will worsen as she grows.

Cystic kidneys in children and adolescents present in various forms and can range from a single cyst to multiple bilateral cysts. In this chapter, a few of the more common disease conditions will be discussed: multicystic dysplastic kidneys, autosomal recessive polycystic kidney disease and autosomal dominant polycystic kidney disease. Other cystic kidney diseases that will not be discussed include nephronophthisis (a common genetic cause of chronic renal insufficiency in children which presents with polyuria and polydipsia, anemia and growth retardation), medullary cystic disease (autosomal dominant disease in which young adults develop renal failure), medullary sponge kidney (dilated intrapapillary collecting ducts and multiple small cysts that usually presents in adulthood), glomerulocystic kidney disease (seen in a variety of inherited syndromes), simple renal cysts (incidental findings that generally do not impair renal function), multilocular cysts (unilateral benign tumor), acquired cystic kidney disease (occurs in patients with renal failure), and syndromes with cystic kidneys (such as tuberous sclerosis, Meckel syndrome, and von Hippel-Lindau disease).

Multicystic dysplastic kidney (MCDK) is usually a benign unilateral disorder of small to large renal cysts separated by dysplastic parenchyma. The shape of the kidney is irregular and normal renal architecture is lost. There are two types of MCDK: the classic type and the hydronephrotic type (1). The classic type contains multiple cysts of various size, with an abnormal renal shape and an atretic proximal ureter. The hydronephrotic type is rarer and consists of peripheral cysts that communicate with a large central cyst with a dilated pelvis and calyces (1).

MCDK is the most common type of renal cystic disease, comprising 10% of fetal uropathies (1). The most recent studies estimate that the incidence is 1 in 2400 livebirths, and it is more common in males (1,2). The disease usually occurs unilaterally, but can be seen bilaterally in as many as 20% of cases (2). MCDK is generally considered to be nonhereditary and sporadic, although rare cases have shown an autosomal dominant inheritance (2,3). Two theories stand out as the most probable causes of MCDK. The first proposes that abnormal induction of the metanephric blastema leads to dysplasia of the renal parenchyma that is non-uniform, resulting in cysts that increase in size and eventually compress normal renal tissue (1). The second theory suggests that MCDK is due to obstruction of the ureter that results in cyst formation (1,3). This theory was exhibited in Beck's experiments of fetal lamb ureter ligations, which resulted in cyst formation in the lambs (1). Urine is usually present in the cysts and causes the cysts to enlarge. In unilateral cases, there is a compensatory hypertrophy in the contralateral kidney.

The most common presentation of MCDK is on prenatal ultrasonography (71% of cases), viewed as early as 16 weeks gestation (1). MCDK usually presents in newborns as a unilateral flank mass, but can occasionally cause vomiting, anorexia and failure to thrive secondary to compressive effects (2). Other possible but rare presentations include urinary tract infection, abdominal pain, hematuria, hypertension, and compromised respiratory function (1,2). MCDK is associated with other anomalies of the urinary tract in half of cases and 15-28% show vesicoureteral reflux in the contralateral kidney (1). There is also an association with contralateral ureteropelvic junction obstruction (1). Other major anomalies can be seen in the cardiac, respiratory and gastrointestinal systems (1). Bilateral cystic kidneys are usually not compatible with life due to oligohydramnios and result in either stillborn babies or newborns requiring dialysis at birth (2). MCDK is diagnosed with ultrasonography but also requires radionuclide imaging to determine functioning of the kidney after 1 month of age (1).

The differential diagnosis for MCDK includes hydronephrosis as well as the other cystic kidney diseases, and may be distinguishable by ultrasound. Hydronephrosis usually retains a reniform shape and shows apparent renal parenchyma around a central cyst (1). Hydronephrosis also retains communication of the cysts with the collecting systems (2). A radionuclide study may need to be performed when distinguishing hydronephrosis from the hydronephrotic type of MCDK. Autosomal dominant polycystic kidneys are usually bilaterally enlarged while autosomal recessive polycystic kidneys are generally small with a hyperechoic pattern.

The management of MCDK is controversial because it is not clear that nephrectomy results in a better outcome. It is recommended to obtain sonography and perform a voiding cystourethrogram within the first 48 hours of life. Radionuclide studies are also performed after 1 month of age to determine renal functioning. Since most cases are asymptomatic, nephrectomy is not always performed and instead close follow-up is maintained. Ultrasound is performed every 3 months up to 1 year of age and then every 6 months up to 5 years of age. Blood pressure is also monitored. Nephrectomy is usually performed only if the child is symptomatic or the parents choose surgery after understanding the benefits and risks.

Unilateral MCDK has an excellent prognosis, especially if there is an absence of other anomalies. In 73% of cases, the cysts decrease in size, with a 40% complete resolution rate (1). However, in 13% of cases, the cysts increase in size and may cause symptoms (1). Uncommonly, children may have pain, infection, or hypertension and even rarer is the possibility of malignant degeneration into a Wilms tumor (1). In the 5% to 17% of cases that are bilateral, newborns generally do not survive and if they do, they require dialysis immediately (1).

Autosomal-recessive polycystic kidney disease (ARPKD) is a recessively inherited disorder that results in bilateral cystic dilation of renal collecting ducts and hepatic fibrosis. The kidneys are enlarged, while retaining their normal shape and have a spongy appearance.

The incidence of ARPKD is believed to be 1 in 6000 to 1 in 55,000 livebirths (4). A single defective gene on chromosome 6p causes ARPKD and is inherited as a typical autosomal recessive disorder (5). Heterozygotes are unaffected. There is a 25% chance of recurrence with subsequent pregnancies. Males and females are equally affected.

Three factors have been shown to contribute to the formation of renal cysts and their subsequent enlargement. The first factor is that tubular hyperplasia is present in all cystic diseases and contributes to cystic expansion (5). Second, secretion of tubular fluid leads to the accumulation of intratubular fluid and progressive enlargement (5). Third, abnormalities in extracellular matrix interactions appear to have an effect on cell growth and can lead to abnormal epithelial hyperplasia and secretion (5).

ARPKD may present with various features but is usually seen within the first year of life (4). Many cases are seen prenatally on ultrasound with oligohydramnios and large renal masses (5). Other presentations include enlarging abdominal masses, respiratory problems due to limited diaphragm mobility (or pulmonary hypoplasia), failure to thrive due to enlarged kidneys, proteinuria, pyuria, hypertension due to fluid overload, and urinary tract infections due to vesicoureteral reflux (4). Children eventually develop chronic renal failure and end-stage renal disease with associated electrolyte imbalances of hyperkalemia and hyperphosphatemia (4). Liver abnormalities may present as signs of portal hypertension such as esophageal varies, hepatomegaly, and spider nevi.

The diagnosis of ARPKD is suspected in children with bilaterally enlarged kidneys and is highly suspected if siblings also have a history of ARPKD. Ultrasound is the diagnostic test of choice, although an intravenous pyelogram will also show enlarged kidneys (4). On renal ultrasound, there is increased echogenicity with a possible hypoechoic rim (4). It is important to rule out autosomal-dominant polycystic kidney disease (ADPKD), nephroblastomatosis and bilateral Wilms' tumor (4). ADPKD usually does not have associated liver abnormalities and the inheritance pattern is dominant instead of recessive (4).

Management of ARPKD involves ventilatory support for respiratory problems due to pulmonary hypoplasia and diaphragmatic compression. Hypertension should be treated with medications, although it may be difficult to control. Urinary tract infections should be properly diagnosed and treated with antibiotics. Chronic renal failure and end-stage renal disease are treated by managing electrolyte abnormalities, anemia, and renal osteodystrophy, with eventual dialysis and transplantation (4). Nephrectomy may be an option if there are respiratory problems and/or feeding problems due to compression (4).

Improvements in technology continue to increase the survival rates of ARPKD. Studies show that about 46% are alive at 15 years of age and those that survive through the first year of life have an even higher survival rate (79% alive at 15 years) (5). Renal failure is the most common cause of death and ARPKD continues to have significant long-term morbidity (4).

Autosomal-dominant polycystic kidney disease (ADPKD) rarely presents in children but occasionally exhibits a severe course in childhood. It is characterized by renal cysts in various locations and extrarenal manifestations in the gastrointestinal and cardiovascular systems. As the disease progresses, renal fibrosis and glomerulosclerosis increase (4). ADPKD is the most common inherited renal disease, occurring between 1 in 500 to 1 in 1000 livebirths (4). Mutations in any one of three genetic loci (PKD1, PKD2, PKD3) result in ADPKD. PKD1 is located on chromosome 16p and encodes the protein polycystin, a transmembrane protein (4). PKD2 is found on chromosome 4q and encodes for polycystin-2, another transmembrane protein that interacts with polycystin (4). There is not much known about PKD3 (4). The variability in cyst formation and disease severity depends on the locus affected and how much protein is being made.

The clinical presentation of ADPKD depends on the age of presentation. Most often, children are asymptomatic and are only diagnosed because of a positive family history and subsequent CT or sonogram. Symptomatic children typically present in late childhood or adolescence with any of the following: hematuria, hypertension, abdominal or flank pain, abdominal mass, urinary tract infection, or proteinuria (4). Symptoms in childhood usually correlate with greater than 10 cysts present (4). The third pediatric presentation is severe neonatal disease that is frequently fatal. These neonates usually die from respiratory failure but they may also die of renal failure during the first year of life (4). Extrarenal manifestations are not common in children but are common in adults. These extrarenal problems include mitral valve prolapse, hypertension, extrarenal cysts, aortic aneurysms, intracranial aneurysms, hernias, colonic diverticula, cholangiocarcinoma, and congenital hepatic fibrosis (4). Intracranial aneurysms are a significant cause of mortality when they rupture (4).

ADPKD is diagnosed with sonogram or CT scan as macroscopic renal cysts. As children age, the number and size of cysts increases and therefore, the sensitivity and specificity of diagnosis by ultrasound increases as children become older (4). ADPKD can often be distinguished from other cystic kidney diseases through family history. Ultrasound can also be used to distinguish ARPKD from ADPKD. ARPKD shows bilaterally enlarged kidneys with microcysts as well as hepatic periportal fibrosis, while ADPKD will show enlarged kidneys with macrocysts as well as extrarenal cysts (4,5).

Management of ADPKD includes physical examination, urinalysis and blood pressure monitoring every 6-12 months (4). Ultrasound should also be performed every 2-3 years (4). Presenting problems of ADPKD should be treated with standard therapy. Chronic renal insufficiency is monitored carefully, especially with respect to its effects on nutrition and growth (4). Hypertension is treated with antihypertensives and urinary tract infections are treated appropriately. Screening for intracranial aneurysms should be performed in teenagers with a family history of intracranial aneurysms due to the serious consequences of rupture (4,5).

Since most children with ADPKD are asymptomatic, the prognosis throughout childhood is generally good. One study showed that 80% of children diagnosed maintained normal renal function throughout childhood (5). As adults, disease progression is variable and unpredictable.

Potter syndrome is variably defined as including congenital renal failure or cystic kidneys associated with oligohydramnios, abnormal facies and hypoplastic lungs. If the fetal kidneys are non-functional or minimally functional, oligohydramnios results since the source of amniotic fluid is fetal urine. Oligohydramnios results in the abnormal facies due to the compression of the developing face against the inner uterine wall. Pulmonary hypoplasia results from large kidneys (due to one of the cystic kidney conditions) compressing the diaphragms, preventing fetal lung development. Congenital bilateral renal agenesis is also included in Potter syndrome. Potter syndrome is generally incompatible with life due to congenital renal failure and pulmonary hypoplasia.

Questions

1. Which renal cystic diseases are inherited? What is the most common inherited renal disease?
2. How can you differentiate between ARPKD and ADPKD?
3. Compare the outcomes of MCDK and ARPKD?
4. What abnormalities besides renal manifestations should a clinician look for on physical examination of a patient with ARPKD?
5. Do extrarenal manifestations of ADPKD usually present in children?

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Answers to questions

1. ARPKD and ADPKD are inherited. MCDK is usually non-heritable. ADPKD is the most common inherited renal disease.
2. ARPKD: bilateral enlargement and microcysts on ultrasound. Hepatic fibrosis is also present in ARPKD. ADPKD: macrocysts and usually involve extrarenal cysts in the liver, pancreas, ovary, and/or spleen. ADPKD will also have a positive family history in a parent and the aunts/uncles on the affected parent's side of the family.
3. Unilateral MCDK has an excellent prognosis with most cases decreasing in size. ARPKD, since it is bilateral, eventually leads to end-stage renal disease.
4. Signs of portal hypertension: spider nevi, esophageal varices, hepatomegaly. There can also be signs of respiratory distress or abnormal feeding due to the compressive effects of enlarged kidneys.
5. No, extrarenal manifestations of ADPKD such as intracranial aneurysms and extrarenal cysts usually present in adulthood.

Chapter XIII.4. Dialysis

James H.E. Ireland, MD
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A 16 year old girl with a past medical history of systemic lupus erythematosus (SLE) presents with intractable nausea and vomiting, increasing edema and no urine output for two days. She had been diagnosed with SLE at age 14. A biopsy of her kidney at that time revealed a diffuse proliferative glomerulonephritis with prominent crescents and minimal fibrosis. Her creatinine at that time was 1.5, and she was started on cyclophosphamide, prednisone and furosemide.

Exam: VS T 36.5, P 110, RR 18, BP 180/110, weight 75 kilograms. She is very nauseated and actively vomiting. She responds to verbal commands and is slightly somnolent, but oriented. She has pale conjunctiva and no oral lesions or thrush. Her lungs are clear. She is tachycardic and has a rub. Her abdomen is soft and nontender and her upper and lower extremities have 1-2+ edema.

Her CBC is significant for a low hemoglobin of 7.5 g/dl with an MCV of 92. Her chemistries show an elevated potassium at 5.7; a low bicarbonate at 13 and a markedly elevated BUN at 119 and a creatinine of 14. Her ANA is elevated at 160 and her TSH is normal. A renal ultrasound shows small echogenic kidneys with no hydronephrosis, masses or stones. A chest x-ray shows engorged pulmonary vessels (fluid overload) and an enlarged heart. An echocardiogram reveals a moderate pericardial effusion, but is otherwise normal. Emergent vascular access is obtained, and she is taken to hemodialysis. She receives dialysis daily and within a week, her symptoms resolve. A follow-up echocardiogram demonstrates a reduction in the pericardial effusion.

The above case illustrates the use of acute hemodialysis for a patient with uremia secondary to chronic renal failure in the setting of SLE. There are a number of indications for acute hemodialysis (HD). One is renal failure (creatinine clearance less than 10) as manifested by a urea nitrogen over 150 mg/dL or a serum creatinine elevated 10-fold over normal, or signs and symptoms of uremia. This may include nausea and vomiting, altered mental status, seizures, pericarditis or bleeding diathesis (platelets become progressively dysfunctional in the setting of uremia). Other indications for HD include uncontrolled hyperkalemia, refractory fluid overload, severe metabolic acidosis, tumor lysis syndrome, certain inborn errors of metabolism, and certain acute poisonings/overdoses.

When a teenager needs HD, vascular access must be obtained prior to initiating therapy. In the acute or emergent setting, a double-lumen catheter (such as a Vas-Cath) can be placed in a large vein. The internal jugular or femoral vein is preferred, but sometimes the subclavian vein is used. This vascular access device has large lumens to permit optimal blood flow. As with any central venous line, there is a risk of pneumothorax if the internal jugular or subclavian sites are used; a risk of bleeding (especially in the uremic patient) and a risk of infection. Although placed with sterile technique, the risk of infection increases the longer the line is kept in place. If kept in for an extended period, infection is one of the drawbacks to having this type of vascular access; however, it can be used immediately and is ideal when dialysis needs to be done quickly.

If chronic, "maintenance" dialysis is planned for some future time (as with chronic renal failure), more permanent vascular access should be established. One method involves connecting a vein to an artery to create an AV fistula. It is usually done in the non-dominant arm, in case ischemia or other complications occur. Once it is decided that permanent vascular access is needed, the patient and nurses should be instructed to make that limb "off-limits" for blood draws, intravenous lines or arterial punctures. This is done to minimize any potential trauma to the blood vessels prior to fistula surgery. As a reminder, a large sign is usually placed above the patient's hospital bed stating "No Draws: Left Arm." A number of artery-vein anastomoses are possible, but the two most common are the wrist radiocephalic and the elbow brachiocephalic. After surgery, the fistula needs about 6 weeks to mature and cannot be used during this time. Maturation is the histologic process of venous thickening and dilating, essentially taking on some of the characteristics of the attached artery. These changes enable the venous portion of the graft to accept the repeated insertion of the dialysis needle. If the patient is already requiring dialysis, a temporary percutaneous double lumen catheter can be used until the fistula is mature and usable. After surgery, the fistula should have a palpable thrill and audible bruit. This should be checked at least daily as an assessment of patency.

If an AV fistula is not anatomically possible, another type of permanent access is an arterial-venous (AV) graft. This involves the use of a synthetic tube to connect the artery and the vein. Common sites for AV grafts include the radial artery to the basilic vein, the brachial artery to the basilic vein and the brachial artery to the axillary vein. Maturity is faster than the fistula, usually occurring in 2-3 weeks. The major drawback of the AV graft is it is much more likely to clot and occlude than the native fistula, due to intimal hyperplasia in the native vein to which the graft is attached. If this should occur, medical therapy (thrombolysis) or a surgical procedure can be done to salvage the graft (interventional procedures or thrombectomy). Both AV fistulas and AV grafts have a number of long-term complications. This includes edema or ischemia of the hand, pseudoaneurysm at the graft or fistula site, infection, thrombosis and congestive heart failure. If a hemodialysis patient has a fever or positive blood cultures and fistula or graft infection is suspected, a nuclear WBC scan can be done to help confirm the diagnosis. Staphylococcus is a frequent infecting organism, but gram negative rods and enterococcus infections can also occur. Empiric therapy should be directed at these organisms, and may require vancomycin coverage for methicillin-resistant Staphylococcus aureus (MRSA). Species of Candida can also infect these sites.

Vascular access in infants and small children is more complicated than in older children and teenagers. In neonates, an umbilical vein may be used. Some hemodialysis machines permit a single lumen or needle to be used. For permanent access, AV grafts may be necessary if native blood vessels are too small to create a fistula.

Once vascular access is established, blood leaves the body via tubing into the dialysis unit. It passes along a semipermeable membrane with a dialysis solution (dialysate) flowing along the other side of the membrane. Solute particles from the blood then pass down their concentration gradient into the dialysate for removal. The mechanism of dialysis can be simplified based on standard diffusion: where particles (solutes) of high concentration (in the blood) move down their concentration gradient to an area of low concentration (the dialysate). The movement is across a semipermeable membrane, so larger particles will cross more slowly or not at all. Thus the smallest particles will be removed the fastest. Also, the steeper the concentration gradient, the quicker the removal. Blood and dialysate run through a filter in opposite directions, with the membrane separating them. This countercurrent flow maximizes the concentration gradients for solute removal. The blood is then returned to the body. Other aspects of the dialysis prescription include the type of membrane, flow rate of blood and dialysate, temperature, length of time on dialysis, and composition of the dialysate. Modern machines can monitor these functions and monitor for potential air emboli and blood leaks in the dialyzer as well.

The dialysate is purified water with precise amounts of various ions and glucose. For example, a typical solution would contain: Na+ 145 mEq/L; K+ 3.5 mEq/L; Ca++ 3.5 mEq/L; Mg++ 0.75 mEq/L; and dextrose 200 mg/L. Different ionic concentrations can be used for different clinical situations. For example, if a stable patient needs routine dialysis, and her pre-dialysis potassium is usually 5.0, a dialysate with 3.0 mEq/L of potassium would be used. If the same patient had a viral gastroenteritis and her pre-dialysis potassium was 3.0 then a dialysate with 4.0 mEq/L of potassium would be used. If that same person was feeling fine and ate some high potassium foods such as fruit the day before dialysis and her pre-HD potassium was 7.0, a dialysate with zero potassium would be used.

Besides normalizing ionic concentrations and removing waste, another function of dialysis is to remove accumulated water. Water moves across the membrane under hydrostatic forces and this is known as ultrafiltration. The degree of that force determines the amount of net water movement. Small particles within the water are also removed during this process, which is called convection. Particles larger than the dialysis membrane pore size will be left behind in the blood.

Major complications of hemodialysis are unusual. These can include: seizures, hypotension and hypothermia. The seizures are a severe manifestation of the dysequilibrium syndrome. The syndrome has a characteristic EEG tracing and in mild cases can be associated with headaches, nausea and vomiting. More severe manifestations include seizures and coma. The cause of the syndrome is unknown, but it may have to do with osmotic shifts in the brain. It can occur during or after hemodialysis. Preventative measures include limiting the flow and the total time on hemodialysis for the first few sessions to prevent large fluxes.

Hypotension is another common complication during hemodialysis. If significant, it can be treated with volume replacement. If fluid removal is necessary, however, more frequent dialysis sessions with smaller volumes removed per session may be required. Additionally, some patients tolerate fluid removal better if dialysate sodium concentrations are increased, something known as sodium modeling. If large changes in fluid status are avoided, hypotension during the session is minimized. Finally, hypothermia can be a problem, as removed blood can be cooled in the tubing and machinery. This is prevented by heating units in the dialysis machine to keep the temperature constant.

As mentioned, hemodialysis can be associated with large fluid shifts that can result in hypotension. When patients are unable to tolerate such a drop in blood pressure or are already on vasopressor support (for example, in septic shock) another form of dialysis may be required. This typically is known as continuous renal replacement therapy (CRRT) or slow continuous therapies. When done via a Vas-Cath, it may also be called continuous veno-venous hemofiltration (CVV-H). This form of dialysis is done continuously (compared to three times a week for 4-5 hours in standard hemodialysis). It is used almost exclusively in the intensive care unit for critically ill patients. This type of therapy is also better than standard hemodialysis for clearing elevated phosphorus seen in tumor lysis syndrome in leukemia or lymphoma, in part because a different and more porous membrane is used.

Another method of dialysis is peritoneal dialysis (PD). In this method, an indwelling catheter is placed in the abdomen, usually under general anesthesia in children, and the PD solution (another form of dialysate) is circulated through the peritoneal cavity. This is the most common method of chronic dialysis for pediatric patients. PD can also be used in the acute setting, but it is not efficient in correcting hyperkalemia, hyperphosphatemia or hyperammonemia and if these values are critical, another dialysis modality should be used. The advantages are that vascular access is not needed; no complicated machinery is required; it does not cause large volume shifts; and it can be performed at home after fairly brief training. In PD, the peritoneum acts as a biological dialysis membrane and solutes cross this from the blood to the dialysate. Fluid can be changed manually every six hours or changed through an automated cycling machine (such as during sleep.) The major complication of this method is peritonitis. Other drawbacks include the presence of an external catheter from the abdomen, which may make children self-conscious.

Long term complications of chronic renal failure in children include growth failure, anemia, hypertension, acidosis and renal osteodystrophy. The etiology of the growth failure is multifactorial. Children may respond to exogenous recombinant human growth hormone. Erythropoietin deficiency accompanies renal failure and results in anemia. Folic acid is usually added as a supplement and ferrous sulfate can be started if iron stores are low. If anemia persists, exogenous erythropoietin can be initiated. Hypertension may be due to dietary indiscretion, inadequate fluid removal during dialysis, or the renin-angiotensin axis. If these cannot be remedied, anti-hypertensive medications are used. Acidosis can interfere with growth hormone function and should be treated with exogenous alkali (calcium carbonate, sodium bicarbonate) to maintain a serum bicarbonate levels of 22 mEq/L or higher.

Renal osteodystrophy can be minimized with careful control of calcium and phosphate metabolism. As the kidney fails, phosphate excretion is impaired and the serum levels rise and a concurrent fall in serum calcium. The lower serum calcium levels stimulate

parathyroid hormone production which acts on bone to release calcium. This can cause bone pain, deformities and growth retardation. Radiographically, osteopenia, epiphyseal slipping and subperiosteal resorption may be present. Laboratory findings can include elevated PTH and alkaline phosphatase with low levels of active vitamin D (1,25-dihydroxy-vitamin-D3). Vitamin D undergoes final hydroxylation and activation in the kidney, which is hampered in chronic renal failure. The reduction in active metabolites of vitamin D results in calcium malabsorption in the intestines and further exacerbates osteodystrophy, and in children with open epiphyses can lead to what is known as "renal rickets". Therapy should reduce excess phosphate by limiting dietary phosphorus to 1 gram per day, and if levels remain high, treatment with binders (calcium carbonate, calcium acetate, or sevelamer) should be initiated. These are given with meals to bind dietary phosphate and prevent absorption. Additionally, calcium and active vitamin D replacement should be optimized and PTH levels should be monitored for hyperparathyroidism.

In summary, dialysis can be a life-saving therapy for acute renal failure, certain poisonings and in severe electrolyte disturbances seen in the tumor lysis syndrome. It can also substitute for native kidneys in patients with end stage renal disease, although children do not thrive as well as they do with a functioning renal transplant. Ideally, dialysis can act as bridge until normal renal function returns or the patient is able to receive a kidney transplant.

Questions

1. What are the indications for dialysis in pediatric patients?
2. What situation is CVV-HD preferred over HD or PD?
3. What are the advantages of PD?
4. What are three complications that may occur in patients undergoing hemodialysis?
5. What are some long term complications of renal failure?

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Answers to questions

1. Renal failure with uremia; BUN over 150 mg/dl; creatinine over 10 mg/dL; severe hyperkalemia; severe acidosis; refractory fluid overload (CHF); certain inborn errors of metabolism; certain acute poisonings; tumor lysis syndrome.
2. In hemodynamically unstable patients.
3. Can be done at home; no complex machinery; no vascular access.
4. Hypotension, seizures, hypothermia.
5. Anemia; acidosis; hypertension; growth retardation, renal osteodystrophy, platelet dysfunction.

Chapter XIII.5. Hemolytic Uremic Syndrome

Jonathan K. Marr, MD

This is a 3 year old male who is brought to the ED by his mother when she noted bloody diarrhea earlier in the day. There is no fever, ill contacts, or recent exposures to children with diarrhea. He is noted to be pale. His family had attended a birthday party 7 days prior where the child had consumed hot dogs and hamburgers.

Exam: VS T 37.7, P 150, R 28, BP 100/45, oxygen saturation 100% in RA. Weight 17 kg (75%ile). He is alert but fussy, pale, and non-toxic appearing. His conjunctiva are pale. His TMs are normal. He has no nasal flaring or palatal petechiae. His oral mucosa is moist and his tongue is pale. His neck is supple without adenopathy. His heart has a regular rhythm with tachycardia and a grade III/VI vibratory systolic ejection murmur at the left sternal border without radiation. No heaves, lifts, thrills, rubs, or gallops are present. His lungs are clear with good aeration. His abdomen is flat, soft, and non-tender, with the liver edge palpable 3cm below the RCM. The spleen is non-palpable. His genitalia and anus are normal (no rectal prolapse). His pulses and perfusion are good. There are is no edema, rash, or petechiae.

Labs: CBC: WBC 16,000 with 56% segs, 12% bands, 27% lymphs, 3% eos, 2% basos, hemoglobin 8 mg/dL, hematocrit 24.6, platelet count 75,000; peripheral smear shows schistocytes, helmet cells, and polychromasia. Na 133, K 5.9, Cl 96, bicarbonate 16, BUN 45, creatinine 1.3, glucose 145 mg/dL, Ca 7.8, PO4 7.1, uric acid 7.3, and LDH 300. Coagulation studies are normal.

Hemolytic uremic syndrome (HUS) is a heterogeneous group of similar entities that has been recognized for over 45 years and has been reported from most parts of the world. It is one of the most common causes of acute renal failure in childhood and is defined by a combination of microangiopathic hemolytic anemia, variable degrees of thrombocytopenia, and renal failure (1). Other systems, such as the CNS may be involved.

HUS can be classified in a number of ways, but the most common is the diarrhea-associated (D+ HUS) versus atypical (D- HUS) HUS without diarrhea. The D+ HUS is characterized by a sudden onset of hemolytic anemia, thrombocytopenia, and acute renal failure after prodromal gastrointestinal enteritis. The atypical (D- HUS) is rare in childhood, portends a worse prognosis, is more likely to relapse, and may be associated with a family history of HUS disease. It appears to be associated with certain chemotherapy drugs (cyclosporin and tacrolimus), oral contraceptives, cancer, bone marrow transplantation, Streptococcus pneumoniae infections, and vasculitic diseases (1).

Another common classification used is Shiga-like toxin-associated HUS (Stx HUS), since D+ HUS has been strongly associated with a toxin-producing strain of Escherichia coli O157:H7 (1,2). Historically, Shigatoxin (Stx) is an exotoxin produced by Shigella dysenteriae type I and the term verotoxin is derived from the use of vero (monkey) cells as a cytotoxic assay for the Shigatoxins produced by E. coli O157:H7 (1). Human verotoxin producing E. coli (VTEC) strains produce one or both of the toxins Stx-1 and Stx-2 and are established causes of HUS associated with bloody diarrhea. Other strains of E. coli besides O157:H7 produce shiga toxins; they include E.

coli O111, O26:H11, and O103:H2, although they are less commonly found in HUS cases, since their assays are not routinely commercially available (1,2).

Epidemiologically, the most common form of the HUS syndrome (D+ HUS) occurs predominantly in healthy children 6 months to 5 years of age, and has seasonal variation with peaks in the summer and fall (1). Most cases of D+ HUS occurring during epidemics are due to ingestion of contaminated, usually undercooked, ground beef. Approximately 1% of beef cattle in the United States harbor intestinal E. coli O157:H7. The organisms become incorporated during the processing of ground beef that mixes meat from multiple cattle such that one infected animal can contaminate large quantities of ground beef. E. coli O157:H7 can also be acquired by consuming fruits or vegetables contaminated by manure, drinking unpasteurized milk, swimming in contaminated lakes, and person-to-person contact (1).

Stx produced by VTEC is most specifically toxic to cells containing a specialized glycolipid receptor called glycosphingolipid globotriosyl ceramide (Gb3) (2). Glomerular epithelial cells in the renal cortex contain large quantities of Gb3. This explains the predilection for renal cortex lesions and acute renal failure (1). Other areas that contain Gb3 include the CNS and the pancreas.

VTEC also releases lipopolysaccharide (LPS), stimulating WBCs to release inflammatory mediators (TNF-alpha, IL-1, and elastase) that cause endothelial cell detachment, increased procoagulant activity, and release of free radicals causing oxidative cell membrane injury (1). The injury to endothelial cells in renal microvessels results in local intravascular coagulation and a microangiopathic hemolytic anemia with mechanical destruction of erythrocytes and platelets by fibrin strands in narrow vessels (1). Platelet adherence contributes to microthrombi and platelets are consumed when platelet-fibrin thrombi are formed in these injured areas. The capillary lumina are narrowed by endothelial swelling and occlusive thrombi, effectively decreasing blood flow to the glomeruli leading to renal insufficiency and eventually progressing to renal failure.

Clinically, HUS presents with abdominal pain, vomiting, and bloody, mucoid diarrhea. The prodromal phase of the illness varies from 1-15 days before the onset of HUS. Pallor and petechiae occurs within 5-7 days after the onset of the bloody diarrhea. Other signs that may be noted include oliguria, personality changes, and drowsiness. The oliguria found in 60% of patients lasts an average of one week; however 50% of patients, are anuric for an average of 3 days. Most patients are irritable and somnolent. Other findings include behavioral changes, ataxia, dizziness, tremors, and twitching. With progression of the disease, anuria, coma, hemiparesis, cranial nerve dysfunction, cerebral infarcts, seizures, and death can occur. Seizures are reported in 3-5% of cases (2). Active bleeding other than the bloody diarrhea is rare. Hypertension is a common feature of HUS and occurs in 50% of all affected individuals. Possible etiologies for this include fluid overload and increased renin activity (1). Pancreatic insufficiency manifested as transient diabetes mellitus occurs in 4-15% of patients (1,2). Mortality has declined and is between 5-10% during the acute phase. Predictive features associated with poorer long-term outcomes include: severe gastrointestinal prodrome (colitis with rectal prolapse), prolonged duration of anuria, extended duration of dialysis, coma on admission, and high leukocyte count (1). Generalized seizures during the acute phase of the disease are not predictive of death or poor neurological sequelae (1). Age and gender have no consistent correlations on outcome.

The differential diagnosis of early HUS includes: ulcerative colitis, Crohn's disease, appendicitis, intussusception, idiopathic rectal prolapse, gastroenteritis, or acute bacterial endocarditis.

Thrombotic thrombocytopenic purpura (TTP), also known as Moschcowitz's syndrome is similar to HUS with the features of: microangiopathic hemolytic anemia, thrombocytopenia, renal dysfunction, fever, and neurological disturbances (4). It is probable that TTP and HUS represent a similar pathological process, except that TTP is the more serious multisystem disorder with a higher mortality (30-40% within 3 months). The pathophysiologic events involved with TTP are not fully understood but probably involve abnormalities in endothelial composition and unusually large von Willebrand Factor (vWF) multimers in the circulation causing platelet activation with resultant platelet thrombi formation.

Laboratory findings in HUS include a negative Coombs test, normochromic, normocytic anemia with helmet cells, schistocytes, and polychromatophilia on blood smear indicative of hemolysis. Other evidence for hemolysis is an elevated LDH and low serum haptoglobin. An unconjugated hyperbilirubinemia is usually present. The mean hemoglobin is 8 mg/dL. The platelet count is moderately depressed to 50,000, but can be as low as 5,000. Neither the severity nor the duration of the thrombocytopenia correlates with the overall severity of disease. The duration of the thrombocytopenia lasts from 2-3 weeks and there are usually no signs of active bleeding other than the bloody diarrhea. The half-life of infused platelets are shorter, as they are likely taken up by the liver and spleen; furthermore, circulating platelets are dysfunctional. Leukocytosis is present and is nonspecific diagnostically; a recent study, however, found the risk of developing HUS proportional to the initial WBC count (3). Coagulation tests are normal and fibrin split products may be positive.

Signs of renal dysfunction include elevated serum levels of creatinine, potassium, phosphorus, and uric acid which result from decreased glomerular filtration, hemolysis, and transcellular cation shifts (1). Elevations in BUN and creatinine may initially reflect volume depletion because of the diarrhea, but may later be the result of renal failure. Sodium, calcium, and albumin may be low from initial diarrhea losses and later from volume overload because of renal failure. Pancreatic insufficiency is manifested by elevations in amylase and lipase or glucose intolerance.

Histopathology on renal biopsy (not always done unless clinically indicated) demonstrates glomerular lesions of endothelial cell swelling and a widened subendothelial space filled with fibrin-like substances and lipids (1). This results in a thickened capillary wall and reduced capillary lumen. The glomerular basement membrane is intact. Occasionally there may be crescents and signs of necrosis and the glomeruli may be lobulated and resemble membranoproliferative glomerulonephritis (1). Thrombi may occlude arteriolar lumens and there may be tubulointerstitial disease. Fibrin, fibronectin, IgM, and C3 are found by immunofluorescent microscopy along capillary walls, mesangium, and in the subendothelial spaces of capillaries and arterioles (1).

Treatment for HUS is supportive. Dehydration should be corrected, but over hydration should be avoided if oliguric renal failure occurs. Fluids must be limited to insensible losses plus the volume of urine output. Hyperkalemia, hyperphosphatemia, and severe metabolic acidosis may be managed medically. Dialysis is indicated if this fails. Packed red blood cells should be transfused if the hemoglobin falls below 6g/dL or for symptomatic anemia. Platelet transfusions are rarely administered since generalized bleeding is not common; however, they may be indicated before surgical procedures (i.e. catheter placement for hemodialysis or peritoneal dialysis) or active bleeding. Hypertension should be treated to prevent encephalopathy or congestive heart failure. Calcium-channel blockers (nifedipine) or nitroprusside are the medications often recommended to control hypertension.

Peritoneal or hemodialysis should be considered when fluid and electrolyte imbalances cannot be corrected by medical management, or when fluid overload compromises cardiac or pulmonary function. In general, when the BUN exceeds 100 mg/dL, dialysis should be considered even in the absence of fluid and electrolyte imbalances (2). Non-oliguric patients generally do not need dialysis.

Antiplatelet drugs, intravenous immune globulin, anticoagulants, thrombolytic agents, prostacyclin, and corticosteroids have not been found to be beneficial (1,2). Plasma infusion or exchange therapy found to be beneficial in patients with TTP, has not been found to be advantageous in patients with HUS. Plasmapheresis has been of benefit in atypical HUS (D-) when neurological involvement is present

(1). Fresh frozen plasma administration may be harmful in patients with HUS (1). Antibiotic therapy during D+ HUS is controversial, after a recent report suggested that the risk of developing HUS may be increased after antibiotic therapy (sulfa-containing and beta-lactam) for E. coli O157:H7 (3). Currently, a chemically synthesized trisaccharide (Synsorb-Pk), was found to bind with high affinity to Stx-1 and Stx-2, and is undergoing human trials in Canada in assessing its value in preventing D+ HUS (1).

Prevention of D+ HUS is most effective by cooking ground beef until the inside is no longer pink. The Food and Drug Administration recommends a minimum internal temperature of 155 degrees F for cooked hamburger. The most effective means of preventing person-to-person spread is supervised handwashing. Infected children must be excluded from day care centers, until they have documented negative stool cultures for E. coli O157:H7.

Prognosis for HUS has improved with the introduction of dialysis. Previously, children with HUS died from fluid overload, metabolic derangements, and uremia. The acute fatality rate ranges from 4-12% and another 5% develop acute renal failure and anuria. End-stage renal disease or chronic renal failure develops in 10-15% of HUS patients (2). 65-85% recover completely, however, a significant number of patients develop renal sequelae (proteinuria, hypertension, and low creatinine clearance) during long-term follow up studies (1).

Questions

1. What is the likely etiology of D+ HUS?

2. What defines HUS?

3. What types of blood cells would be most consistent with a diagnosis of HUS in a 3 year old child with bloody diarrhea?
   a. Atypical lymphocytes
   b. Elliptocytes
   c. Myeloblasts
   d. Schistocytes
   e. Spherocytes

4. What is the strongest indication for dialysis?
   a. Serum sodium of 120
   b. Initial bicarbonate of 14
   c. Serum BUN 120 mg/dL
   d. Initial K of 5.2
   e. Anuria for 3 days

5. True/False: The severity of hemolysis correlates with degree of renal failure?

6. A 3 year old girl presents with signs and symptoms of intussusception which include crampy intermittent abdominal pain, crying with puffy eyes, currant jelly diarrhea, pallor, dehydration and oliguria. Could this patient have HUS? Explain how all of the findings above could be due to HUS instead.

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Answers to questions

1. E. coli O157:H7
2. Microangiopathic hemolytic anemia, thrombocytopenia, and renal failure.
3. d. schistocytes
4. c. serum BUN >100
5. False
6. Crampy abdominal pain (due to colitis), crying with puffy eyes (due to abdominal cramps, fluid retention due to renal failure causing puffy eyes), currant jelly diarrhea (actually bloody diarrhea due to E. coli O157:H7), pallor (due to hemolytic anemia), dehydration (due to diarrhea), oliguria (due to renal failure).

Chapter XIII.6. Urinary Tract Infection
Janet M. Berreman, MD

This is a 4 month old female who presents to the office with a chief complaint of fever, vomiting, and loose stools. She has had tactile fever for 3 days, and had 5-6 episodes of emesis on the first day of illness. Stools were liquid on the first and second days of illness. She was seen at an emergency room 2 days ago, where the impression was gastroenteritis. No labs or x-rays were done in the emergency department. She returns to the office now because of persistent fever. Vomiting and diarrhea have resolved, but she is breast-feeding less well than usual. Her mother notes that her urine seems "strong" and that she is not as playful as usual. She has had no known ill contacts. She has no cough, URI symptoms, or rash. Past history is unremarkable and she is on no medications.

Exam: VS T 38.9, P164, R40, Wt. 5.3kg (15%ile, and 150gm below her pre-illness weight). She is alert, smiling, active, not toxic, and in no distress. Her anterior fontanelle is soft and flat. Her eyes and ENT exams are normal. Her oral mucosa is moist. Her neck is supple. Heart rate is regular without murmurs. Lungs are clear and her respirations are non-labored. Her abdomen is flat, soft, non-tender, without hepatosplenomegaly or masses. Her external genitalia are normal. Her skin is warm and well perfused, with no rash. Her back exam reveals no deformities or cutaneous defects. Her neurologic exam shows normal tone, strength, and activity.

A urine specimen obtained by transurethral catheterization yields a small amount of cloudy urine, which is positive for leukocyte esterase and nitrite tests. This is sent for culture. Her CBC shows a WBC 9.4, H/H 9.3/27.5, platelets 389,000, 51% neutrophils, 44% lymphocytes, 3% monocytes, 2% eosinophils. She is given 250mg of ceftriaxone intramuscularly and is scheduled for recheck in the office the next morning.

At follow-up the next day, she is smiling and non-irritable, and shows a 250 gm weight gain. She fed well overnight and continued to have a low grade fever. Urine culture is positive for greater than 100,000 colonies/ml of a non-lactose fermenting organism, with identification and sensitivities pending. Ceftriaxone is repeated at the same dose. The following day, she is afebrile and her parents feel that she is entirely back to normal. Urine culture result identifies E. coli, sensitive to all antibiotics tested. She is started on oral trimethoprim-sulfamethoxazole (TMP-SMZ) to complete 10 days of antibiotic therapy. She remains well on oral antibiotics. Following 10 days of therapy, she is changed to a prophylactic dose of TMP-SMZ and a renal ultrasound and voiding cystourethrogram (VCUG) are scheduled. Both studies are normal. Repeat urine cultures on day 3 of antibiotics, and again at the time of VCUG are negative. Antibiotics are discontinued. She has done well without recurrent episodes of UTI.

Urinary tract infections (UTIs) are a common, potentially serious, and (especially in young children) often occult bacterial infection of childhood. During childhood, UTI occurs in approximately 3-5% of girls and 1% of boys. Most of the UTIs in boys occur in the first year of life, whereas the age of the first diagnosed UTI in girls is highly variable. After 2 years of age, UTI in females exceeds that in males by a factor of 10:1 (1). Uncircumcised males less than one year old are more likely to be affected than circumcised males (2,3). The prevalence of UTI in a febrile child 2-24 months of age, without other source of infection, is 5% (4). After 6 years of age, and before the onset of sexual activity, incidence of UTI falls dramatically in both sexes.

Many factors may predispose a child to UTI, including abnormalities of the urinary tract such as vesicoureteral reflux (VUR), renal anomalies with hydronephrosis or obstruction, neurogenic bladder, or nephrolithiasis; functional abnormalities such as constipation, fecal incontinence, or incomplete bladder emptying; and environmental factors such as bubble baths, poor perineal hygiene, pinworms, or sexual activity, including sexual abuse. Labial adhesions in girls and phimosis in boys also contribute to an increased risk of UTI.

UTI causes acute morbidity as well as long term sequelae including hypertension and impaired renal function. Accurate diagnosis of UTI is important both to facilitate appropriate management of the acute illness, and to insure appropriate evaluation and follow-up. Equally important is accurately ruling out a UTI to avoid unnecessary, costly, and potentially harmful treatment and evaluation.

The clinical presentation of UTI varies greatly, primarily with the age of the child. In general, the older the child, the more clearly signs and symptoms point to the urinary tract. Thus older children (over 6 years) and adolescents are likely to present with dysuria, urgency, or frequency, and may have associated fever, chills, flank pain, enuresis, or hematuria. Younger children (2-6 years) can have any of these same signs and symptoms, but they may show more nonspecific signs such as abdominal pain, altered voiding pattern, decreased appetite, or general malaise (5).

From infancy to 2 years of age, fever alone is the most common presentation of UTI (6). There may be associated vomiting, diarrhea, constipation, poor feeding, irritability, or late-onset jaundice, but these features do not aid in distinguishing UTI from other causes of fever. Vomiting and diarrhea are frequently attributed to gastroenteritis, when in fact it is a UTI. A history of malodorous urine or crying with urination is helpful when present, but absence of these complaints does not rule out UTI. In this age group, UTI should also be considered in the differential diagnosis of failure to thrive. The possibility of UTI should be considered in any febrile (temp greater than 39 degrees C, 102.2 degrees F) child under 24 months of age, keeping in mind that girls under 24 months of age, and boys under 6 months of age are at highest risk.

The diagnosis of UTI depends upon: first, maintaining a high index of suspicion for the condition, especially in young children and infants; and second, performing appropriate diagnostic studies.

Physical examination of the child with suspected UTI focuses first on assessing the overall degree of illness severity (relatively stable or possibly toxic and septic) of the child, including hydration status, level of alertness and comfort or discomfort, and perfusion state. Vital signs must be evaluated, especially for fever, hypertension (as a sign of renal impairment), signs of shock, and weight (for chronic failure to thrive or acute weight loss suggestive of dehydration). The abdomen should be carefully examined for any masses or tenderness, including costovertebral angle (CVA) tenderness. Genitalia should be examined for signs of trauma, urethral or vaginal discharge, labial adhesion, or phimosis. Rectal examination may provide further assessment of any intra-abdominal masses or tenderness, and assessment of rectal tone may aid in ruling out a neurologic abnormality which could contribute to UTI susceptibility. Visual inspection of the sacral spine for skin dimples or other cutaneous abnormalities may similarly lead the clinician to further evaluate the child for spinal cord abnormalities associated with a neurogenic bladder.

The diagnosis of UTI requires culture of a properly collected urine specimen (7). In children less than 2 years of age, a properly collected urine specimen requires an invasive procedure: either suprapubic aspiration or transurethral catheterization. As children advance in age and toileting abilities, it becomes possible to obtain a clean catch mid-stream voided urine specimen and thus avoid invasive collection techniques. A clean catch mid-stream urine sample means that the urethral meatus and surrounding area should be clean, and that the urine collected should be from the middle of the stream: i.e., the first few drops of urine should not be collected. For girls, cleaning involves separating the labia and cleaning the area (usually with a series of 3 pre-moistened antiseptic towelettes). For

circumcised boys, the glans of the penis should be similarly cleansed. For uncircumcised boys the foreskin is gently retracted prior to cleaning. After cleaning, the child voids over the toilet, with the parent "catching" the urine in a clean specimen cup after the first few drops are passed. In girls this is often more easily accomplished by having the child sit facing backwards on the toilet, so the parent can easily catch the urine stream from behind the child.

Urinalysis (UA) is helpful in evaluating the likelihood of UTI, but cannot definitively rule it in or out. The most readily available and useful components of the UA in this context are the leukocyte esterase test, nitrite test, and microscopy. Sensitivity is markedly improved when all three are used, although specificity is lower. A positive leukocyte esterase or positive nitrite test is suggestive of UTI, as are more than 5 WBC per HPF (high power field) of a spun urine specimen, or bacteria present on a gram stain of an unspun urine (a test not done by most labs unless specifically requested).

Urine culture results are expressed quantitatively, indicating the colony-forming units (CFU or colony count) of bacterial growth. The significance of a positive culture depends upon the method of specimen collection and the number of colonies of a single organism (8). In general, a colony count of greater than or equal to 100,000 is considered positive on any properly obtained urine specimen. Colony counts of greater than or equal to 10,000 on a catheterized specimen are also considered positive. Colony counts of 1,000 to 10,000 on a catheterized specimen are suspicious and should be repeated. A specimen obtained by suprapubic aspiration should be sterile, so any growth of gram negative bacilli or any more than a few thousand gram positive cocci is considered a positive culture.

Urine specimens obtained from young children by means of a bag applied to the perineum have a high rate of contamination. A negative culture of a bag-collected urine does rule out a UTI; however, a positive culture obtained in this way is not a definitive diagnostic test. In fact, positive culture results from such a specimen are estimated to be falsely positives as much as 85% of the time (7).

The most common causative agents of UTI are gram negative colonic bacteria, with Escherichia coli being the cause of most acute UTIs (1,8). Klebsiella, Proteus, and Enterobacter species are other common gram negative causes of UTI. Gram positive organisms include Staphylococcus species and Enterococcus species. Cystitis may be viral, usually caused by adenovirus (1,9).

UTIs are divided into two major classifications: those that involve the lower urinary tract (cystitis) and those that involve the upper urinary tract (pyelonephritis). Lower tract disease typically does not cause fever, and does not result in renal damage. Upper tract disease classically causes fever, abdominal or flank pain, and in younger children and infants the nonspecific signs of irritability, poor feeding, malaise, failure to thrive, or vomiting and diarrhea. The differentiation of upper tract disease from lower tract is primarily a clinical one, with supporting evidence provided by technetium (Tc 99m) dimercaptosuccinic acid (DMSA) scanning (10) and by elevated C-reactive protein (CRP) values (9).

The differential diagnosis of UTI varies with the age and presenting complaints of the patient. The nonspecific signs associated with UTI in infancy and toddlerhood may be associated with bacterial sepsis originating in any site, as well as with gastroenteritis, hepatitis, or viral infection. Signs of cystitis in older children or adolescents raise the possibility of chlamydial or gonorrheal urethritis. The presenting complaints of pyelonephritis must be differentiated from acute appendicitis, hepatitis, gall bladder disease, pelvic inflammatory disease, and other causes of acute abdominal pain.

Treatment of UTI depends upon assessment of the likelihood of the diagnosis of UTI and the clinical severity of the illness. These assessments will guide the clinician to: await culture results before initiating antibiotic therapy; initiate empiric oral antibiotic therapy; initiate empiric parenteral outpatient therapy; or hospitalize for empiric parenteral therapy. Initial treatment decisions are made before culture results are available, and are therefore empiric. The goals of prompt treatment are eradication of the acute infection, symptom resolution, prevention of progression of disease (e.g., to pyelonephritis, abscess, or sepsis), and reduction of the risk of renal scarring and its long term sequelae (7,11).

When therapy is initiated empirically, the clinical condition of the child is the primary factor considered. In every case, an adequate urine specimen for culture must be obtained prior to initiating therapy. The younger and/or more clinically ill the child with probable UTI is, the more aggressive initial therapy needs to be. In the non-toxic appearing, usually older child, in whom there is a relatively low suspicion of UTI, and no concern of upper tract disease, treatment may be deferred until urine culture results are available. A non-toxic child, who is feeding well, is well-hydrated, and for whom compliance and follow-up are not problematic, is appropriately managed with oral antibiotics and close outpatient follow-up.

At any age, a child with signs of urosepsis, severe clinical illness, or significant dehydration should be hospitalized for parenteral antibiotic therapy and close clinical monitoring and supportive care. High risk children, such as those with immunologic impairment or known urologic abnormalities, may also need hospitalization. Inpatient therapy traditionally has been recommended for all children with suspected pyelonephritis as well as for infants less than 1 year of age with UTI. Some of these children may be managed with outpatient parenteral antibiotics, or even with oral antibiotics (7,11,12), if compliance and close daily follow-up can be assured. Children who are vomiting, or otherwise unable to reliably take oral medications, or for whom compliance is a concern, should be treated parenterally (either as inpatients or outpatients) until these issues are resolved (7,13).

The initial choice of antimicrobials is guided by the chosen route of administration, known uropathogens, and any compromise of renal function of the patient. It is adjusted based on clinical response and results of culture and sensitivity testing. Initial oral therapy may be with a sulfonamide (TMP-SMZ or sulfisoxazole) or with a cephalosporin (cephalexin or cefixime are commonly used). Parenteral therapy may be with a cephalosporin (ceftriaxone, cefotaxime) or ampicillin and/or an aminoglycoside (used with caution in the setting of impaired renal function). The oral drug nitrofurantoin is excreted in the urine, but it does not reach therapeutic concentrations in blood or tissues. It therefore should not be used to treat febrile UTIs in infants, or to treat pyelonephritis.

The choice of initial oral empiric therapy involves consideration of spectrum, side effects, allergies, palatability, dosage schedule, and price. TMP-SMZ is often considered the drug of choice. It is, however, associated with some risk of Stevens-Johnson syndrome, and can precipitate hemolysis in patients with undiagnosed G6PD deficiency. Cephalexin is the most palatable of the three, and the least expensive, but usually dosed QID. Cefixime is the most expensive, but offers the advantage of once a day dosage. TMP-SMZ is intermediate in price, and dosed BID. All three have excellent coverage for the usual pathogens. Any of these drugs is an acceptable first choice. Amoxicillin should no longer be considered a first line drug for empiric therapy, due to increasing resistance of E. coli to amoxicillin/ampicillin.

Clinical response to therapy is generally prompt, with improvement evident within 24-48 hours of initiating antimicrobial therapy. If clinical improvement is seen, and culture results indicate that the uropathogen involved is sensitive to the antimicrobial being used, routine repeat culturing of the urine after two days of therapy is not necessary. However, if sensitivities are unavailable, are intermediate or resistant, or the expected clinical improvement is lacking, repeat culture should be obtained.

Children started on parenteral antibiotics may be changed to an oral antibiotic when they are clinically well enough to do so. That is, when they are non-toxic, well-hydrated, afebrile, and tolerating oral intake. Again, oral antibiotic choice is guided by the results of initial culture and sensitivity testing of the urine.

Duration of therapy varies somewhat, again based on age and degree of illness of the child. Any child or infant with a febrile UTI needs a total of 7-14 days of antibiotic therapy, with 10-14 days preferred for those with clinical evidence of pyelonephritis (7). Short course therapy (3 days or less) is reserved for adolescent females with uncomplicated cystitis (11).

The management of UTI does not end with the successful treatment of the acute infection. Rather, it continues with the evaluation for renal anomalies or VUR, monitoring for recurrence of UTI, short or long term antibiotic prophylaxis to prevent recurrence, and medical or surgical management of any underlying predisposing conditions.

Children with VUR are at increased risk of renal damage from UTIs, as are children with other anomalies of the urinary tract. Therefore, all children (with the exception of adolescent females with uncomplicated cystitis) with a documented UTI should be investigated with a renal ultrasound and VCUG (14,15). These studies may be performed as soon after the diagnosis of UTI as is convenient. Delaying studies for 3-6 weeks after the acute infection (as previously recommended) does not alter the detection of VUR, but does substantially decrease the likelihood that the studies will be completed (16).

If studies are delayed until after completion of 7-14 days of antimicrobial therapy, the child should remain on antimicrobial prophylaxis until the studies are completed. Drugs of choice include TMP-SMZ, sulfisoxazole, and nitrofurantoin, in doses adjusted for prophylaxis rather than therapy (7,17).

The child with VUR needs long term follow-up with antibiotic prophylaxis, periodic monitoring of urine cultures, repeat imaging of the urinary tract, and possible surgical consultation (for persistent VUR, high grade VUR, or recurrent UTIs despite prophylaxis) (14,18). DMSA scanning is helpful in determining the presence of renal scarring in children with VUR and thus can assist in management decisions.

Prognosis after UTI in childhood depends on: 1) whether the infection was limited to the lower tract (cystitis) or involved the upper tract (pyelonephritis), 2) the presence or absence of VUR, and 3) the presence or absence of other urinary tract anomalies, especially those with obstructive uropathy.

Uncomplicated infections without associated VUR or obstruction respond well to antimicrobial therapy. However, as many as one third of these patients may experience recurrence of UTI within the first year after acute infection (19). Follow-up urine cultures (generally monthly for 3 months, then at 3 month intervals X 3, and then at 6 month intervals X 2) are therefore recommended.

VUR is present in 30-50% of children with UTI (20). Its severity is graded on a scale of I, II, III, IV, V (14). While pyelonephritis and renal scarring can occur in the absence of VUR, the severity of renal scarring correlates with the degree of reflux (20). The natural history of low grade reflux is toward spontaneous resolution, whereas high grade reflux is less likely to resolve without surgical intervention. The combination of renal parenchymal infection (especially repeated infections) and VUR or obstructive nephropathy puts children at risk for renal scarring which may progress to chronic renal insufficiency, hypertension, reflux nephropathy, and end stage renal disease (9,14,20). Early diagnosis and treatment of UTI and VUR or obstruction may diminish the incidence of these long term complications (21).

In summary, appropriate management of UTI hinges on three essential factors, all of which are the responsibility of the clinician: 1) Maintaining a high index of suspicion for the diagnosis, especially in infants and toddlers who rarely have specific symptoms, 2) Properly obtaining an adequate urine specimen for culture before initiating antimicrobial therapy, 3) Following through on the patient's clinical response, culture and sensitivity results, and the results of imaging studies and follow-up cultures. Careful attention to all of these points will optimize the diagnosis, treatment, management, and outcome of the child with UTI.

Questions

1. When is it appropriate to treat empirically for UTI without first properly obtaining an adequate urine specimen for culture?
2. What factors affect the decision of how to obtain a urine specimen when UTI is being considered? How will the method of collection affect the interpretation of culture results? When is a urine specimen obtained by bag collection a definitive test for UTI?
3. What are some host and pathogen factors contributing to the development of UTI?
4. How is pyelonephritis distinguished from lower tract UTI? What is the importance of making the distinction?
5. What is the commonest clinical presentation of UTI in the child under 2 years of age? What are some associated signs and symptoms which may be present?
6. Which clinical features of UTI are reason to consider parenteral therapy and/or hospitalization?
7. How would you explain to parent and child the technique of obtaining a clean catch mid-stream urine sample: in girls and in circumcised and uncircumcised boys?
8. Familiarize yourself with the technique of transurethral bladder catheterization (22) in male and female infants and toddlers, including: a) Prevention of specimen contamination, b) Selection of appropriate equipment, c) Relevant anatomic landmarks, and d) Possible complications.

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Answers to questions

1. Empiric treatment for UTI should not be initiated without first obtaining an adequate specimen for culture. The only pediatric exception would be a child so severely ill (in septic shock and/or anuric) that waiting to obtain a urine sample could be life threatening. One might consider empiric treatment without culture in an uncomplicated older teen, however, such patients are rarely "uncomplicated" when considering issues such as recurrence, sexually transmitted diseases, etc.

2. The method of obtaining a urine specimen is affected by the patient's age, severity of illness, state of cooperation, toileting abilities, and whether or not antibiotics are to be started empirically. The colony count considered positive varies with the collection method: any growth with suprapubic aspiration; greater than or equal to 10,000 CFU for a catheterized specimen; and greater than or equal to 100,000 CFU for a clean catch specimen. Bag specimens are only definitive when culture result is negative (and therefore should not be used if empiric therapy is to be initiated).

3. Host factors contributing to development of UTI include uncircumcised male, labial adhesions, poor hygiene, constipation, urinary tract obstruction, dysfunctional voiding patterns, and neurogenic bladder. Pathogens are those commonly found in the vicinity of the urethra: skin and GI organisms, as well as blood-born organisms in the neonate. The strains of E. coli which commonly cause UTI show increased adherence to uroepithelial cells.

4. Classical signs of pyelonephritis include CVA tenderness, fever, and signs of systemic illness, while lower tract disease is milder and may present with only urinary urgency, frequency, or dysuria. Abnormal DMSA scan or elevated CRP results support the diagnosis of pyelonephritis.

5. The commonest presentation of UTI in the child under two years of age is fever. Associated signs and symptoms may include vomiting, diarrhea, irritability, poor feeding, malodorous urine, oliguria, constipation, or jaundice.

6. Empiric parenteral therapy and/or hospitalization should be considered when suspected UTI is associated with signs of urosepsis, severe clinical illness, dehydration, immunologic compromise, or urologic abnormality. Vomiting, poor oral intake, or concerns for poor compliance are also reasons to use parenteral therapy.

7. "Clean catch mid-stream" urine sample means that the urethral meatus and surrounding area should be clean, and that the urine collected should be from the middle of the stream: i.e., the first few drops of urine should not be collected. For girls, cleaning involves separating the labia and cleaning the area (usually with a series of 3 pre-moistened antiseptic towelettes). For circumcised boys, the glans of the penis should be similarly cleansed. For uncircumcised boys the foreskin is gently retracted prior to cleaning. After cleaning, the child voids over the toilet, with the parent "catching" the urine in a clean specimen cup after the first few drops are passed. In girls this is often more easily accomplished by having the child sit facing backwards on the toilet, so the parent can easily catch the urine stream from behind the child.

8a. Transurethral catheterization is an invasive procedure and is performed using standard sterile technique, including povidone/iodine wash of the periurethral and perineal areas, sterile field, sterile gloves, and sterile catheter and specimen cup.

8b. Infant feeding tubes in #5 or #8 french size are adequate for most infants and toddlers. It is not necessary or advisable to use a Foley catheter, as there is no need for a balloon. The catheter is removed as soon as the sample is obtained.

8c. The catheter is introduced into the urethral meatus, and advanced gently until there is return of urine. This is done with the infant in the supine, "frog-leg" position. The catheter tip may be lubricated with sterile lubricant or sterile water. In circumcised boys the urethral meatus is easily seen. In uncircumcised boys it is usually revealed by gentle retraction of the foreskin (if not, the foreskin is retracted as far as is easily possible and the catheter introduced with gentle probing until the meatus is located). The urethral meatus may be less easy to see in infant girls. It is helpful to remember that it lies anterior to the vaginal introitus, and to be familiar with the often fleshy appearance of the infant hymen. Separation of the labia, adequate light, and familiarity with the appearance of the genitalia facilitate locating the urethral meatus. A frequent error is introduction of the catheter into the vagina (recognized by the absence of urine return and by resistance to gentle advancement of the catheter beyond a couple of centimeters). Some practitioners opt in this situation to leave the misdirected catheter in place while a second catheter is introduced into the urethra (using the first catheter to "block" or mark the vaginal introitus). Whether or not the first catheter is left in place, a new sterile catheter must be used for the second attempt, to avoid contamination with vaginal flora.

8d. Complications of urethral catheterization include doubling back of the catheter (either in the urethra or in the vagina), trauma to the urethral meatus or mucosa, and possible introduction of infection. There can be subsequent stricture formation. Familiarity with the anatomy and avoidance of any forceful catheter advancement can minimize the risk of complications. A lubricated catheter of appropriate size should advance easily through the urethra. Any resistance should be taken as a sign to retract the catheter rather than to advance it more forcefully. The risk of introduction of infection is minimized by careful adherence to sterile technique.

Chapter XIII.7. Hydronephrosis and Reflux
Robert G. Carlile, MD

Case 1

A term newborn male infant is noted to have unilateral hydronephrosis on prenatal ultrasound. At 3 days of age, a renal and bladder ultrasound shows a normal right kidney, and a moderately severe left renal hydronephrosis, with no dilation of the ureter. The bladder is normal. A voiding cystourethrogram is obtained at 6 weeks of age which shows no evidence of vesicoureteral reflux, and no posterior urethral valves. Urinalysis, complete blood count, electrolytes, BUN, and creatinine are normal. At 4 weeks of age, a Mag3 renal scan with furosemide (Lasix) washout shows equal split function (right kidney 50%, left kidney 50%). The t-1/2 (washout half time) shows normal washout on the right, and prolonged washout on the left.

The patient is placed on surveillance with serial renal ultrasounds and renal scans for the next 2 years. At 2 years of age, he develops left sided abdominal pain, nausea and vomiting, without fever or chills. A renal ultrasound shows worsening left hydronephrosis and a renal scan shows diminished left renal split function to 35% (the right split function is now 65%), and markedly prolonged left renal half-time. The right renal half-time is normal.

He undergoes a left pyeloplasty at 2 years of age, and does well post operatively. A Mag3 renal scan is done 3 months postoperatively, which shows the left renal split function to have returned to 45% (right 55%), with the washout half time to have normalized. A renal ultrasound postoperatively shows only minimal residual hydronephrosis.

Case 2

A 3 year old female infant presents with fever (T 39.6), nausea, vomiting, and left flank and abdominal pain, as well as dysuria. A CBC shows a WBC of 20,000, with a left shift. Urinalysis shows 50 to 100 WBCs per high power field. Intravenous fluids and IV antibiotics are administered with clinical improvement. Urine culture later grows out greater than 100,000 colonies of E. coli. A renal ultrasound shows normal kidneys (no hydronephrosis). She is discharged home on a full course of oral antibiotics for 2 weeks, which is then changed to once daily trimethoprim/sulfamethoxazole (TMP/SMX) prophylaxis thereafter.

A VCUG (voiding cystourethrogram) shows left Grade II vesicoureteral reflux. She is continued on suppressive TMP/SMX daily with no further UTIs. A nuclear cystogram 1 year later shows persistence of the reflux, and the suppressive antibiotics are continued. A subsequent nuclear cystogram one year later shows resolution of the reflux. The antibiotic prophylaxis is stopped, and the patient has no further problems with febrile UTIs/pyelonephritis.

For the pediatrician, hydronephrosis has become a finding to be encountered even before the child enters their care, with many children being diagnosed antenatally with prenatal ultrasonography. Hydronephrosis is the most common congenital condition that is detected by prenatal ultrasound and represents 50% of all abnormalities (1). The incidence of detectable urinary dilation in utero can be as high as 1 per 100 pregnancies but only 20% of these may be clinically significant postnatally. 50% of antenatal cases detected after 28 weeks gestation have postnatal imaging that is normal (2). The majority of cases detected prenatally will resolve either before the end of pregnancy or within year 1 of life (1).

Hydronephrosis in the older child is often found incidentally during the work-up for nonspecific abdominal complaints (3). Historically, prior to the extensive use of ultrasound, neonates with hydronephrosis presented with a palpable abdominal mass, urinary tract infections, urinary retention, hematuria, feeding difficulties, or failure to thrive (4,9).

With regards to ureteral development, in week 5 of gestation, the ureteral bud develops as a posterior diverticulum of the mesonephric duct. This ureteral bud penetrates the adjacent metanephric blastema inducing the formation of the metanephric kidney, and forms the urinary collecting system (ureter, renal pelvis, calices, and collecting ducts). As the ureters develop, they become temporarily obstructed, then undergo a physiologic recanalization along their middle portion. Acquisition of smooth muscle begins at the ureterovesical junction (UVJ) and proceeds cephalad. Recanalization is completed by day 41 of gestation. Urine formation begins at 10 weeks of gestation. It is believed that many of the dilations observed in the neonatal period represent ureteral distention in response to transient obstruction that occurred in utero. The levels at which these are suspected are the ureterovesical junction, the mid ureter, and at the ureteropelvic junction (1,3).

Failure of the ureteral bud to stimulate development of the metanephric blastema may result in multicystic, dysplastic kidneys, which may be confused with a hydronephrotic kidney. Unilateral multicystic, dysplastic kidney is the most common cystic disease of the newborn and the second most common infant abdominal mass after hydronephrosis. The left kidney is more commonly involved. There is no sex predilection or familial tendency (5).

Vesicoureteral reflux refers to the retrograde flow of urine from the bladder into the upper urinary tract. It occurs at a rate of 1 per 1000 in the general population, but is 8 to 40 times more frequent in families with a history of reflux in a sibling. It will be found in 50% of infants and 30% of children with a UTI (5). Of those diagnosed with neonatal reflux, there is a male predominance, whereas females predominate when diagnosed after the newborn period. The average age for diagnosis of reflux is 2 to 3 years (7).

Vesicoureteral reflux may occur because the ureteral bud arises ectopically, leading to a laterally placed ureteral orifice and short submucosal bladder tunnel, which allows reflux. Reflux may also occur if there is incomplete or delayed development of the intrinsic smooth muscle of the distal ureteral segment (5,6). Vesicoureteral reflux predisposes an individual to pyelonephritis by facilitating the transport of bacteria from the bladder to the upper urinary tract. The immunologic and inflammatory reaction caused by a pyelonephrotic

infection may result in renal injury or scarring. Extensive renal scarring causes reduced renal function and may result in permanent renal damage or renal failure (7).

Vesicoureteral reflux is graded as follows: Grade I results in urine reflux into the distal ureter only. Grade II results in urine reflux into the ureter and the renal pelvis, without ureteral dilation and no distension of the renal pelvis (i.e., normal calices). Grade III results in urine reflux into the ureter and the renal pelvis, causing mild hydronephrosis (defined as mild dilation of the renal pelvis and blunting/dilation of the calices) and mild hydroureter (dilation of the ureter). Grade IV results in moderate hydronephrosis and hydroureter. Grade V results in severe hydronephrosis and severe hydroureter.

An ectopic ureter is defined as a ureter that drains into any location other than the bladder trigone. Embryologically, the delayed entry of the ureteral bud into the bladder results in a more distal and medially positioned ureteral orifice. In some instances, the ureter may not even incorporate itself into the bladder but may enter other structures. In females, this may include the urethra, introitus, vagina, uterus, and fallopian tube. In males, the ectopic ureter may enter the bladder neck, prostatic urethra, epididymis, seminal vesicles, or vas deferens. 70% of ectopic ureters are associated with duplicated collecting systems, with 30% found in non-duplicated systems. Ureteral ectopia in a duplicated system is 6 times more common in females than males. Ureteral ectopia in a non-duplicated collecting system is more common in boys (8).

Ureteroceles are a cystic dilation of the distal ureter at the level of the ureteral orifice (intravesical ureter). It results from a failure of normal distal ureteral development. Ureteroceles are more common in females than males by a ratio of 4:1. 80% of ureteroceles are associated with a duplex system and arise from the upper pole moiety. These upper pole segments usually demonstrate varying degrees of renal dysplasia (8).

Posterior urethral valves (a congenital membrane that obstructs or partially obstructs the posterior urethra) occur in boys (1 per 5000 to 8000), with greater than 50% diagnosed in the first year of life. It is felt that the etiology is failure of regression of the terminal segment of the mesonephric duct, which is normally represented by the plicae colliculi, which results in a congenital membrane that obstructs or partially obstructs the posterior urethra (5,6,9).

The Eagle-Barrett Syndrome (Prune Belly Syndrome, Triad Syndrome) is characterized by a dilated, non-obstructed urinary tract, deficiency of abdominal wall musculature (a visibly obvious deficiency of abdominal wall musculature with a distinct flabby abdomen), and bilateral cryptorchidism (undescended testes). The incidence is 1 per 35,000 to 50,000 live births with 95% of the cases occurring in boys. The syndrome is a result of in utero urinary tract obstruction and a specific mesodermal injury between the 4th and 10th week of gestation. GU anomalies that most commonly occur are renal dysplasia or agenesis, vesicoureteral reflux, and a large capacity poorly contractile bladder. Cardiac, pulmonary, and orthopedic anomalies are common in these patients (6).

Older children and adults who present with calculi, flank pain, nausea and vomiting, hematuria, non-specific abdominal complaints, especially if intermittent in nature, during periods of high urine flow, may have ureteropelvic junction obstruction (3). Daytime incontinence, infrequent voiding, poor urinary stream, chronic severe urinary frequency, and complicated enuresis may suggest bladder outlet obstruction (from urethral obstruction or posterior urethral valves) (9).

Many patients with vesicoureteral reflux (VUR) have been discovered prenatally by detection of fetal hydronephrosis, although the diagnosis of VUR is not made until postnatal studies are performed. 80% of these neonates are boys, and most have more severe reflux than do females with VUR discovered after UTI. 80% of reflux diagnosed after UTI occurs in females (7). Children may present with clinical pyelonephritis, fever, abdominal/flank pain, malaise, nausea, vomiting, cystitis with dysuria, frequency, urgency, and urge incontinence.

Patients with ureteral ectopy and/or ureteroceles may be picked up initially with prenatal ultrasound. They may also present at an older age with febrile UTIs, incontinence, hematuria, failure to thrive, abdominal pain, or pelvic pain. Ureteroceles may also present with a palpable abdominal mass or cystic intralabial mass (the result of a large ureterocele that has prolapsed through the urethral lumen) (8).

For the infant noted to have hydronephrosis on prenatal ultrasound, an ultrasound on day 2 of life should be performed. Ultrasound is the mainstay of screening and can provide excellent morphological evaluation in experienced hands. The degree of hydronephrosis and caliectasis can be seen, together with the renal size, parenchymal thickness, and some subjective assessment of the renal cortical texture. Cortical cysts, calcifications, and corticomedullary junction can be noted. The presence and morphology of the contralateral kidney, and the distal ureter should be evaluated. A careful evaluation can rule out distal ureteral dilation, eliminating the necessity of an IVP or retrograde contrast study of the ureter (1). Renal and ureteral duplication may be noted on ultrasound, as well as the presence of a ureterocele in the bladder. If there is no dilation, then a repeat ultrasound is done at one month. If no hydronephrosis is present at one month of age, the evaluation can then stop.

A voiding cystourethrogram (VCUG) is done if hydronephrosis persists after birth. If the patient is a male, has hydroureteronephrosis, a thick walled bladder, and/or posterior urethral valves are suspected, then a VCUG should be obtained immediately (1). The presence of a bladder outlet obstruction is readily established on VCUG. Posterior urethral valves show a characteristic appearance of a prominent bladder neck, dilated posterior urethra, and a bulging membrane at the distal aspect of the verumontanum. The bladder is usually thickened, with trabeculation and diverticula (9). Vesicoureteral reflux may also be present. Ureteroceles may be evident. If valves are present, cystoscopy should be done and the valves resected.

If posterior urethral valves are not suspected, then antibiotic prophylaxis is begun, and a VCUG, and diuretic renography obtained at 4 to 6 weeks.

The VCUG may show vesicoureteral reflux. Reflux grade is important because more severe reflux is associated with higher rates of renal injury, and treatment success varies with reflux grade (7). Follow-up cystography is done using radionuclide cystography because radiation exposure is less than with standard contrast cystography.

Diuretic renography (Mag3 or DTPA radioisotopes) provides information on renal function, with the early uptake of tracer by a kidney indicative of separate renal function ("the split function"). It can also show obstruction by demonstrating the washout from the kidney, augmented by the administration of a diuretic 20 minutes after administration of the initial tracer (1,3). The initial transit of the tracer through the kidney reflects renal perfusion and the amount of tracer accumulated in each kidney 1 to 3 minutes after injection is proportion to its GFR. The differential function (i.e., split function) of each kidney can be calculated. A diuretic is administered IV once the collecting systems are full with the radioisotope. Sequential images, computer generated time-activity curves, and calculated half-times will determine the degree of washout of the tracer in the area of interest. Prolonged washout times (called washout half-times) are often associated with true urinary tract obstruction.

Diminished renal function is definitely present when the split function is less than 35% to 40% (10), while good renal function is demonstrated by split function values of 45% to 50%. A poor washout half-time is greater than 20 minutes, and a good washout half-time is less than 10 to 12 minutes.

A DMSA (another renal isotope) renal scan is useful for the evaluation of cortical renal scarring and patients with VUR. Following an episode of pyelonephritis, renal scarring is usually apparent in DMSA scans within 3 months, but may not be apparent in IVP or ultrasound until 1 to 2 years later (7).

Excretory urography (IVP-intravenous pyelography) is especially performed in the older infant and child. It defines the collecting systems anatomy well, and can be very useful with ectopic kidneys, duplicated kidneys, and ureters, as well as with megaureter. A CT scan is also useful for imaging the renal and ureteral anatomy, and CT angiography can be used to image crossing vessels at the ureteropelvic junction (UPJ). Urodynamics (bladder function studies) are indicated when a functional obstruction is suspected (neurogenic, or non-neurogenic). Patients with spinal dysraphism should be evaluated with urodynamics.

Serum blood chemistries, especially creatinine, are also useful in these patients, and should at least be obtained early on to help establish baseline renal function.

It is important to emphasize that imaging studies cannot be taken and evaluated in isolation, but must be evaluated in conjunction with the other imaging, laboratory, and clinical findings over time, especially with a period of observation (with serial studies), before definitive surgery is considered.

Ureteropelvic junction obstruction is the most common cause of congenital hydronephrosis. US or IVP will show a dilated renal pelvis, and calyces without ureteral dilation. Diuretic renography/renal scan will show an obstructive pattern (prolonged washout half time). Vesicoureteral reflux may be present in some children with UPJ obstruction (11). In the older child presenting with vague abdominal complaints, renal ultrasound, IVP, and/or CT scan will show a dilated renal pelvis and calyces, without ureteral dilation.

Ureterovesical junction obstruction is the second most common cause of congenital hydronephrosis. Hydronephrosis is noted, along with associated ureteral dilation on renal US and/or IVP. Renal scan may show an obstructive pattern. Dilated ureters (megaureters) are divided into three primary categories: refluxing megaureters, obstructed megaureters, and non-obstructed, non-refluxing megaureters. An uncommon fourth primary variety is the refluxing, obstructed megaureter. Secondary megaureter may occur because of extrinsic processes such as tumors, retroperitoneal fibrosis, and vascular malformation. Another cause is functional ureteral obstruction such as with neuropathic bladder disease in those with spinal dysraphism (12). VCUG is helpful in the differentiation of the above categories.

Posterior urethral valves are the most common cause of lower urinary tract obstruction and occurs in males. The prenatal US may show hydroureteronephrosis, bladder thickening, and oligohydramnios. The newborn physical exam may reveal a palpable distended bladder, a palpable prostate on rectal exam, poor urinary stream, and signs and symptoms of renal and pulmonary insufficiency. Renal US shows hydronephrosis and a thickened bladder. VCUG is diagnostic for posterior urethral valves. There is associated reflux in 30% of patients (6).

In females, the most common cause of anatomic bladder outlet obstruction is a ureterocele that has prolapsed into the urethra (urethral prolapse may resemble a large doughnut shaped mass in the perineum). 90% of cases are associated with the upper pole of a complete duplicated collecting system (7). This condition has also been observed in males. Renal ultrasound may show findings similar to those found with posterior urethral valves, as will VCUG and renal scan. The renal US and/or VCUG will also clearly show the ureterocele.

Primary vesicoureteral reflux may present initially as hydronephrosis in the newborn. VCUG is diagnostic, and renal scan shows a non obstructive pattern. It tends to be of higher grade and with a male predominance when presenting in the newborn period (11).

Other causes of hydronephrosis or apparent hydronephrosis, are the multicystic, dysplastic kidney, ectopic ureter, megacalycosis, simple renal cyst, urachal cyst, ovarian cyst, hydrocolpos, sacrococcygeal teratoma, bowel duplication, duodenal atresia, anterior meningocele, and the prune belly syndrome (1).

Ureteropelvic junction obstruction repair (open pyeloplasty) is recommended when there is the morphological appearance of UPJ obstruction on US or IVP, no evidence of distal ureteral distension, and renal function depressed to less than 35% of total renal function. Neonates with better than 35% renal function are followed with repeat scans at 3 to 6 months, then at 12 months of age, and surgery is indicated only when there is clear deterioration in renal function (1). 75 to 85% of infants followed in this manner with observation did not require surgery (1,10). Most patients being followed with observation received antibiotic prophylaxis (1).

Older children, and adults, who present with a symptomatic UPJ obstruction will need repair, and can be considered for laparoscopic and endoscopic treatment of their UPJ obstruction, in lieu of an open pyeloplasty (3). The success rates of open pyeloplasties are greater than 95%.

Ureterovesical junction obstruction/megaureters in the newborn can be managed with observation (with serial US and renal scans) and antibiotic prophylaxis, in those whose renal function is greater than 35% (1). Indications for surgical repair (open ureteral reimplant, sometimes with tapering), include deterioration of renal function, breakthrough pyelonephritis, pain, or calculus formation (12). When a ureterocele is present, the best initial management is endoscopic incision of the ureterocele (1,8).

Posterior urethral valves should be treated in the neonatal period. Treatment is centered on securing adequate drainage of the urinary tract, initially by placement of a urinary catheter and later, by primary cystoscopic ablation of the valves, vesicostomy, or upper urinary tract diversion. The long-term outcome is dependent upon the degree of renal dysplasia present. Associated vesicoureteral reflux should be treated with antibiotic prophylaxis. Persistent bladder dysfunction should be treated with anticholinergics, alpha blockers, and clean intermittent catheterization, as indicated (6,8).

Primary vesicoureteral reflux is managed with antibiotic prophylaxis. Penicillin in the neonate, and TMP/SMX or nitrofurantoin in the older infant and child, is generally administered once daily at a dose calculated to be 1/4th to 1/3rd of the dose necessary to treat an acute infection. Reflux tends to resolve over time as the intravesical segment of the ureter elongates, with the greatest rate of spontaneous resolution occurring in the lowest grades of reflux (approximately 15% per year) (6,7,11). Follow-up cystography is generally performed every 12 to 18 months. The radionuclide cystogram is performed by many because the radiation done to the gonads is lower than with a standard cystogram. In addition, periodic upper tract imaging studies (US, IVP, renal scan) are often performed to detect renal scarring and growth. Many clinicians treating children with reflux obtain urine specimens, periodically for UA and/or culture (7,11).

Medical management with antibiotic prophylaxis is considered successful if the child remains free of infection, develops no new renal scarring, and the reflux resolves spontaneously. Failure of medical management is indicated by breakthrough UTIs, the development

of new renal scars, or the failure of the reflux to resolve. Noncompliance and allergic reactions to the prescribed medications may also lead to failure of medical management (7).

Failure of medical management/antibiotic prophylaxis is an indication for surgical repair of the refluxing ureter. Open surgical management (ureteral reimplant) involves modifying the abnormal ureterovesical attachment to create a 4:1 to 5:1 ratio of length of the intravesical ureter to ureteral diameter. This corrects the reflux in 98% of patients who undergo ureteral reimplantation for Grades I to IV reflux, and in 80% of those who undergo reimplantation for Grade V reflux (7).

Ectopic ureters are treated surgically based upon whether the patient presents with single or duplex systems, how well each moiety functions, and whether there is ipsilateral lower pole reflux. Partial nephrectomy and ureterectomy are indicated for upper pole moieties that are nonfunctioning or very poorly functioning (less than 10% of total function). In those with upper pole function and no evidence of lower pole reflux, ureteropyelostomy or high ureteroureterostomy are reasonable approaches. Ureteral reimplant (ureteroneocystostomy) is a good option for patients with upper pole function and lower pole reflux (8).

The management of ureteroceles is similar to ectopic ureteral management in that the approach taken is dependent upon many variables (single or duplex systems, ipsilateral or contralateral reflux, obstruction, and degree of function present). The goals of surgery are to preserve renal function, correct obstruction and reflux, eliminate urinary stasis and infections, and preserve urinary continence with minimal morbidity and mortality (8). Management options include observation, transurethral incision of the ureterocele, upper pole nephrectomy with partial ureterectomy, ureteroneocystostomy with ureterocele excision, high ureteroureterostomy, and transvesical ureterocele repair.

Prune Belly Syndrome (Eagle-Barrett Syndrome) treatment involves optimization of urinary tract drainage, management of renal insufficiency, and antibiotic prophylaxis. Surgical repair of reflux, orchiopexy, and abdominal wall reconstruction is performed later in childhood (6).

Multicystic, dysplastic kidneys are followed by serial ultrasounds. They do not benefit from antibiotic prophylaxis (1). They involute over time. Most urologists observe the multicystic, dysplastic kidney. There are proponents of excision of these kidneys due to a risk (albeit a very small risk) of malignant transformation.

Fetuses with mild to moderate hydronephrosis are generally observed prenatally. Although there are some centers that treat severe hydronephrosis prenatally related to obstructive uropathy, this is very controversial. The consensus is that intrauterine intervention should be considered only if persistent or progressive oligohydramnios develops in a fetus with a normal karyotype, there are no other life threatening anomalies, and fetal immaturity that precludes delivery (2,6). These procedures should only be performed at tertiary referral centers with extensive experience with fetal surgery.

The widespread use of obstetrical ultrasound has resulted in the detection of antenatal hydronephrosis as a common presentation of congenital renal, ureteral, bladder, and urethral anomalies. Neonatal evaluation and treatment of these congenital urinary anomalies allows the preservation of renal function, the relief of obstruction and reflux, the elimination of infection, and the preservation of urinary continence, to a much greater degree than was possible prior to the advent of prenatal US. Patients with hydronephrosis and/or reflux have an excellent prognosis today.

Questions

1. What is the most common congenital condition detected by prenatal US?
2. What is the initial imaging study that should be done to evaluate a newborn with a history of antenatal hydronephrosis?
3. What further studies should be obtained in a 2 day old male with US findings of hydroureteronephrosis, and a thick walled bladder? What diagnosis is suspected and what is the appropriate treatment?
4. What are the two most common causes of newborn hydronephrosis and how are they distinguished one from another?
5. What further tests should be ordered for the infant, with a history of prenatal hydronephrosis which persists on US on day 2 of life?
6. What are the options for treatment of UPJ and/or UVJ obstructions?
7. What is a ureterocele?
8. What is the cause of primary vesicoureteral reflux?
9. How does antibiotic prophylaxis for the management of vesicoureteral reflux prevent renal scarring?
10. What are the indications for surgical treatment of primary vesicoureteral reflux?

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Answers to questions

1. Hydronephrosis represents 50% of all abnormalities detected with prenatal US.

2. A renal and bladder US should be obtained on day 2 of life. US done earlier may yield a false negative (no hydronephrosis) due to low urine output not distending the collecting systems. If it is normal, then the US should be repeated at 1 month of age, and be normal before considering the hydronephrosis to have resolved.

3. A VCUG should be obtained to evaluate for posterior urethral valves. If PUV are present, the VCUG will show a prominent bladder neck, a dilated posterior urethra, with a bulging membrane at the distal aspect of the verumontanum. The bladder may be thickened. Reflux may be present. The treatment is centered on securing adequate drainage of the urinary tract; initially by placement of a urinary catheter, and later by transurethral ablation of the valves. A vesicostomy (surgical formation of a cutaneous bladder stoma) may be done as a temporizing measure if the infant cannot undergo transurethral ablation of the valves.

4. Ureteropelvic junction (UPJ) obstruction is the most common cause, with ureterovesical junction (UVJ) obstruction being the second most common cause of congenital hydronephrosis. They are distinguished by the fact that with UPJ obstruction, the ureter is not dilated, whereas the ureter is dilated with UVJ obstruction.

5. The infant should be placed on antibiotic prophylaxis (with penicillin) and a VCUG and diuretic renal scan done at 4 to 6 weeks of age.

6. In infants noted to have good (35 to 40% or greater) split function on the renal scan, then serial ultrasound and diuretic renal scans (at 3 to 6 months of age, then at 12 month of age) may be used to follow the patient nonsurgically, on antibiotic prophylaxis. If there is renal function deterioration, breakthrough UTIs, or symptoms of renal colic, then surgery (pyeloplasty in UPJ obstruction, and ureteral reimplant in UVJ obstructions) is indicated. Only 25% of children with UPJ obstructions will require conversion to surgical management.

7. A ureterocele is a cystic dilation of the distal ureter at the level of the ureteral orifice. A ureterocele which has prolapsed into the urethra is the most common cause of congenital bladder outlet obstruction in females. Transurethral incision of the ureterocele is a minimally invasive treatment for symptomatic ureteroceles.

8. The ectopic insertion of the ureter into the bladder wall laterally results in a short intravesical ureter (a short submucosal bladder tunnel), which acts as an incompetent valve during urination, allowing urine to reflux back up into the ureter.

9. The antibiotic prophylaxis sterilizes the urine, and thus prevents bacteria ascending up the refluxing ureters, from causing pyelonephritis and renal scarring/damage. This allows time for normal growth and development of the ureter and bladder to occur. With growth, lengthening of the submucosal bladder tunnel/intravesical ureter results in the resolution of reflux over time, particularly in those with lower grades of reflux. Observation includes serial cystograms (usually nuclear scintography) every 12 to 18 months.

10. The failure of medical management (and thus the need for ureteroneocystostomy) is indicated by breakthrough UTIs, the development of new renal scars, or the failure of reflux to resolve over time. Non compliance or allergic reactions to the prescribed antibiotics may also lead to the failure of medical management.

Chapter XIII.8. Circumcision
Robert G. Carlile, MD

A mother gives birth to a term male infant with a normal penis (no evidence of hypospadias or penile chordee). Testes are descended bilaterally and normal to palpation. The parents are do not want their child to be circumcised. This is not a problem until he is 12 years old, in 7th grade. Since the majority of his male friends are circumcised, he desires circumcision. This is performed by a urologist, under anesthesia, in the operating room. He recovers without any complications. However, the parents are distraught when they learn their medical insurance will not pay the $3,000 bill for this "cosmetic" procedure.

Circumcision is the most common operation performed on males in the United States. It is estimated that 1.2 million newborn males are circumcised in the United States at an annual cost of between $150 and $270 million (1). Sixty percent of boys in the United States undergo circumcision. In Scandinavia and Great Britain, it is rarely performed in newborns (2). Ritual circumcision has been part of Jewish and Muslim faiths.

The prepuce develops in the 10th week of fetal development as a small epithelial tag at the penile tip. At 12 weeks this tag becomes a pronounced fold and grows inward and vertically, surrounding the glans at birth. This fold's inner epithelial layer is fused with the glans' epithelium. The urethra must close before the prepuce (the foreskin covering the glans) completely develops (3). With incomplete urethral closure (hypospadias), the ventral development of the prepuce is incomplete and one will find a thinned or absent ventral foreskin in hypospadias. At birth, the preputial aperture (opening or meatus of the foreskin) is adequate for voiding.

At birth, the prepuce (foreskin) is retractable in only 4% of boys. By 3 years, 90% of the boys' foreskin can be completely retracted (4). At age 17, 99% of the boys can retract their foreskin (3). This progressive separation of the foreskin epithelium from the glans epithelium is caused, in part, by an enlarging accumulation of trapped desquamated cells called smegma (3). This smegma is not to be confused with infection. The prepuce should not be forcibly retracted as spontaneous separation will occur physiologically.

The decision on whether to circumcise a newborn male is controversial. The Task Force on Circumcision of the American Academy of Pediatrics stated that newborn circumcision is not recommended and that the procedure is not essential to the child's current well-being (1). However, there is compelling evidence that newborn circumcision protects against penile cancer, local infection, phimosis, urinary tract infection, and human immunodeficiency virus (HIV) infection (5).

Pediatricians, obstetricians, and family practitioners perform the vast majority of newborn circumcisions in the United States. Circumcision is contraindicated if any penile anomaly is found such as; hypospadias, epispadias, chordee, or micropenis (stretched penile length <2.5 cm). Also, neonatal circumcision is contraindicated with significant prematurity, illness, blood dyscrasia, or family history of a bleeding disorder.

The three methods most commonly used involve the Gomco clamp, the Bronstein (Mogen) clamp, or the Plastibell. In all, the penis is first examined and the preputial adhesions to the glans are lysed with a probe or clamp (2).

The Gomco clamp uses a metal bell placed over the glans with the redundant foreskin pulled over the bell and through the clamp. The clamp is screwed down tightly onto the bell and the foreskin excised. The Bronstein clamp is used in ritual Jewish circumcision and involves pulling the prepuce (foreskin) forward causing the glans to retract slightly. The clasp is locked across the redundant foreskin, and the foreskin is excised. Both the Bronstein and Gomco clamps achieve hemostasis by clamping, crushing, and sealing the skin edges that are left after the foreskin is excised. Electrocautery should never be used with these clamps, as the current could be transmitted to the entire penis, via the metal clamp, and result in penile necrosis.

The Plastibell is a plastic ring that is placed over the glans (inside the foreskin) to the coronal sulcus, and the foreskin is pulled over it, usually after a dorsal slit is made. A large silk suture is tied over tightly onto a groove in the ring. The foreskin is excised, and the ring is left in place (after the handle is broken off). This ring minimizes blood loss, and it falls off in 3 to 7 days.

Local anesthesia with lidocaine (plain) is generally recommended as a dorsal penile nerve block or a ring block in the performance of newborn circumcision (2,6).

The post operative complication rate of circumcision is between 0.2 and 0.6%. These complications include bleeding, infection, phimosis, concealed penis, skin bridge formation, ring retention, meatitis, urethral stenosis, chordee, inclusion cysts, penile lymphedema, urethrocutaneous fistula, hypospadias and epispadias formation, penile amputation, and penile necrosis (3,4). The two most common are bleeding and infection.

Minor bleeding and infection can be managed by primary care physicians, but a low threshold for obtaining a urologic consultation should be maintained for complication management.

Questions

1. What does neonatal circumcision protect against?
2. What are the 3 most common methods used to perform neonatal circumcision?
3. What are the 2 most common complications of neonatal circumcision?
4. What are the contraindications to performing a newborn circumcision?
5. Will you perform newborn circumcision? Why or why not?

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Answers to questions

1. Penile cancer, balanitis, phimosis, urinary tract infection, reduced risk of HIV.
2. Gomco clamp, the Bronstein (Mogen) clamp, and the Plastibell.
3. Bleeding and infection.
4. Hypospadias, chordee, epispadias, penile torsion, micropenis, significant prematurity, blood dyscrasia, or family history a bleeding disorder.
5. Yes or no; see reasons associated with each answer. Yes, because it protects against penile cancer, etc., (see #1). No, because of the risks of complications of infection, bleeding, concealed penis, penile adhesions, meatitis, fistula formation, penile amputation and penile necrosis.

Chapter XIII.9. Enuresis
Potenciano Reynoso Paredes, MD

This is a 4.5 year old male who presents to the office with his mother with a chief complaint of bed-wetting twice a week. Essentially he is healthy except for an occasional cough and fever that the mother attributes to exposure to other children with colds. Urinary discharge occurs at night only and he therefore has to wear diapers to bed. His mother is worried since his brothers and sisters were all toilet trained by this age. There is no history of dysuria, intermittent daytime wetness, polyuria, or polydipsia.

His past medical history is unremarkable. Family history is significant for his father being a bed-wetter. His child development is normal.

Exam: VS T 37, P 110, R 20, BP 107/64, Ht 102 cm (25th percentile), Wt 16.2 kg (25th percentile). He is alert and active, in no distress. His appearance is non-toxic. HEENT and neck exams are negative. His lungs are clear bilaterally. His heart has a normal rate and rhythm, normal S1and S2, and no murmurs or rubs. No masses, organomegaly, or tenderness are appreciated on exam of his abdomen. Bowel sounds are present. He has no inguinal hernias. He has a circumcised penis of normal size. The meatus is normally placed, without discharge. No phimosis is present. His testes are descended bilaterally and are of normal size (Tanner stage 1). His back is straight with normal posture with no scoliosis or tenderness, or midline defects. His extremities and muscle tone are normal. His gait is normal. He is able to hop, skip, and stand on each foot for 5 seconds, copy a square and get dressed without help. His speech and behavior are age appropriate.

You reassure his mother that bladder control is usually attained between the ages of 1 and 5 years and bed-wetting becomes less frequent with each passing year. You recommend that she be supportive of her son's dry nights and avoid criticism of wet nights. You also recommend avoiding excessive fluid intake two hours before bedtime and emptying his bladder at bedtime. He returns to your office after 6 months and his mother feels that the bed-wetting problem has improved significantly. On his next appointment (4 months later) his mother reports the resolution of his bed-wetting problems.

Enuresis, commonly known as bed-wetting, is the most common childhood urologic complaint encountered by pediatricians. Nocturnal enuresis (NE) is defined as involuntary passage of urine during sleep beyond the age of expected continence which is approximately 5 years of age. There are two types of NE. Primary is when a child never stopped wetting for any lengthy period, whereas secondary is acquired enuresis after being dry for at least 6 months. Primary enuresis affects the large majority of children with enuresis.

Since urinary continence is reached earlier in girls than in boys, NE is 2-3 times more frequent in boys. At age 5, 20% have NE at least once a month, with 5% of boys nightly and less than 1% of the girls nightly. Since most NE is due to maturational delay, there is a significant resolution or improvement as the child gets older. Approximately 15% resolve each year. Interestingly, family studies show a strong genetic predisposition for enuresis. More recently studies suggest a genetic linkage of primary nocturnal enuresis to the short arm of chromosome 13.

Organic causes of bed-wetting account for less than 5% of all cases; with most being urinary tract infections. Other organic problems include: diabetes mellitus, diabetes insipidus, nocturnal seizures, genitourinary anomalies, nocturnal ADH deficiency, hyposthenuria (constant secretion of dilute urine) associated with sickle cell disease, medications, or emotional stress. These children need to be recognized and treated. Some children with severe constipation may compress the bladder and present with bed-wetting. Other theories suggest reduced bladder capacity or sleep disturbance.

The office evaluation of NE must exclude any organic causes. A careful history is taken which should include pattern of wetting, developmental milestones, fevers, polydipsia, polyuria, and prior urinary infections. Questioning about sickle cell disease, food allergy, and constipation is occasionally helpful. Attention should also be paid to family dynamics and stresses that may uncover psychological factors.

Physical examination should focus on the neurological, genital, bladder and bowel exams. Back examination should include a search for neurological involvement such as a midline defect or suggestions of an occult spinal dysraphism. A neurological examination that includes gait, muscle tone, strength, and perineal sensation should be done. Examination of external genitalia for abnormalities such as labial adhesions, meatitis, epispadias, and hypospadias should also be done. If possible, and the urine stream sounds abnormal by history, physicians should watch children void. The abdomen should be assessed for evidence of fecal impaction, organomegaly, or bladder distention.

The purpose of initial laboratory tests is usually limited to ruling out infection as the source of the problem. A specific gravity of 1.015 or greater rules out diabetes insipidus and the absence of glycosuria rules out diabetes mellitus. In cases in which urinary tract obstruction or neurogenic bladder are suspected, a voiding cystourethrogram may be warranted.

At present there is no treatment modality that is 100% successful. Again, parents need to be reminded that a majority of bed-wetting is due to maturational delay and not under conscious control. Therefore, the most important aspects of treatment are reassurance and protection of the child's self esteem. It is important that bed-wetting not be perceived as a bad behavior since punishment not only lowers the child self esteem, but also does nothing to improving symptoms. Early education of the parents in regards to maturational delay, role of genetics and the importance of a supportive toilet training practice may ease the difficult period. Remember that there is a 15% spontaneous remission every year so many advocate an approach of reassurance and watchful waiting. Some simple life adjustments such as improving access to the toilet, avoiding excessive fluid just before bedtime and emptying the bladder at bedtime may be tried initially.

To some families, this conservative approach (which requires patience) can lead to suffering and frustration. Instead, a comprehensive method of treatment that includes bladder training, pharmacologic therapy and behavior modification with an alarm system can be implemented.

Treatment can begin with positive reinforcement such as keeping a calendar and rewarding dry nights. Another treatment is bladder training consisting of different methods such as holding urine as long as possible then when the child does urinate he/she is suppose to stop and start the urine flow frequently. Another method is going to the bathroom several times a night, or having the parents wake the child several times during the night and subsequently lengthening the time interval between waking. The objective is to increase the muscle strength of the urethra as well as give the child confidence that he or she can control urine flow and link the feeling of a full bladder with the need to go to the bathroom. Average bladder capacity in children can be approximated by the formula: volume in ounces (30 ml per ounce) = 2 + age in years. Adult bladder capacity is about 250 to 400 ml.

Pharmacologic therapy consists of tricyclic antidepressants (imipramine) or desmopressin acetate (DDAVP). Each has advantages and disadvantages. Imipramine has anticholinergic effects on bladder capacity and noradrenergic effects which decrease bladder detrusor excitability. 10-60% respond favorably to imipramine treatment, but more than 90% relapse. Imipramine is also potentially lethal with acute overdose (especially cardiac toxicity). DDAVP is a synthetic analog of vasopressin stimulating water retention and urine concentration, thereby reducing urine volume. DDAVP is available in two forms, tablets and nasal spray. The oral form is often used on children with nasal congestion such as colds and allergies. The drawback is the cost and rare mild side effects of DDAVP. DDAVP is useful in certain situations such as a child going to overnight camp. There is a 25-50% success rate with DDAVP, but a relapse rate of 94%.

In recent years, enuresis alarms have been shown to be the most effective treatment for bed-wetting. Urination acts as a stimulus for the alarm and wakes the patient from sleep. The cure rate is 60-80% and it has the lowest relapse rate of 10-40% when compared to other treatments. The only drawback is that the child and family must be highly motivated to stay committed to these conditioning methods.

Questions

1. At what age do parents usually become concerned about bed-wetting?
2. True/False: Most nocturnal enuresis is due to organic causes.
3. Which drug for nocturnal enuresis is cardiotoxic?
4. What laboratory test should be done to evaluate a child with enuresis?
5. What is the bladder capacity of children?
6. In evaluating a chronic bed-wetting child, what should you look for in an abdominal exam?
7. True/False: Enuresis alarms produce excellent results if the child wakes up spontaneously when the alarm goes off.

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Answers to questions

1. Typically at age 5 or 6 years.
2. False.
3. Imipramine.
4. Urinalysis with specific gravity, glucose, protein, blood and white cells.
5. Most adults have a bladder capacity between 250-400 ml, but the average bladder capacity in children can be approximated by the formula: volume (oz.) = 2 + age in years.
6. The abdominal exam should asses for masses secondary to enlarged urinary organs (bladder, kidney) and for evidence of palpable stool in the colon suggesting fecal impaction.
7. True.

Chapter XIII.10. Acute Scrotum
Robert G. Carlile, MD

A 10 year old male presents with a chief complaint of acute onset of left scrotal pain 3 hours earlier, which awoke him from sleep. The pain is constant and does not change with position. There is no history of trauma. He has no dysuria, fever, chills, nausea or vomiting.

Exam: He is afebrile in moderate distress secondary to left scrotal pain. The left hemiscrotum is edematous and erythematous. The left testicle has a transverse lie, with marked tenderness to palpation. The cremasteric reflex is absent on the left. The right hemiscrotum and testicle are normal on exam. The circumcised penis is normal, with no urethral discharge present.

A CBC and urinalysis are normal (this results in an unnecessary delay of one hour). Color Doppler ultrasound scanning of the scrotum demonstrates the absence of blood flow to the left testicle and epididymis. Normal blood flow to the right testicle is present. No testicular masses are noted.

An emergent urological consultation is obtained. Scrotal exploration, under anesthesia, reveals a 720 degree torsion of the left spermatic cord, an ischemic testicle, and a "bell-clapper" deformity. With detorsion, the left testicle's normal color returns. The left testicle is then "fixed" to the scrotal wall to prevent retorsion. The right testicle is also fixed to the scrotal wall. Post-operatively, his pain was markedly relieved with the detorsion of the left testicle, and the remainder of his recovery is unremarkable.

The acute scrotum is a true urologic emergency. The window of opportunity to salvage a torsed, ischemic testicle is only 6 hours (1). Acute scrotal swelling should be considered testicular torsion until proven otherwise.

Puberty is the most common age at which testicular torsion occurs, with the newborn period being the second most common. The incidence is 1 in 4000 males younger than 25 years (2).

Testicular torsion can be classified into two types, relative to the tunica vaginalis' relationship to the area of the spermatic cord that twists: extravaginal and intravaginal. Extravaginal torsions occur perinatally, during testicular descent and prior to testicular fixation in the scrotum (2). This incomplete fixation of the gubernaculum (the fibrous cord extending from the fetal testis to the fetal scrotum which occupies the potential inguinal canal and guides the testis in its descent) to the scrotal wall allows the entire testes and tunica free rotation within the scrotum (3). The rotation of the cord is "extravaginal" because the rotation of the cord is proximal to the attachment of the tunica vaginalis that encloses the testes. These comprise 5% of all testicular torsions (4).

Intravaginal torsion occurs in the remaining 95% of all testicular torsions (4). A congenital high attachment of the tunica vaginalis on the spermatic cord allows the testes to rotate on the cord, within the tunica vaginalis. This is the "bell-clapper" deformity which is a horizontal lie of the testicle instead of the normal vertical lie. It is called a bell clapper deformity because the testicle resembles a horizontal oval hanging from a cord at its midpoint (like the clapper in a bell) as opposed to the normal testicle which resembles the letter "b" or "d" with the testicle positioned vertically attached to the cord on its side. This deformity is commonly bilateral, which places the contralateral testicle at risk for torsion also (3). As viewed from below, the testes rotate inward or medially during a torsion; the right clockwise and the left counter clockwise.

The acute onset of severe testicular pain with associated nausea and vomiting is very suggestive of testicular torsion, especially in the adolescent. Fever and dysuria are not common in testicular torsion. Intermittent testicular torsion is suspected when brief episodes of acute testicular pain occur recurrently. Torsion of a testicular or epididymal appendage (appendix testis or appendix epididymis) usually presents in mid childhood with mild discomfort of a few days duration (2).

Epididymitis and/or orchitis, on the other hand, may be associated with fever, dysuria, and a more gradual onset of scrotal pain, usually over several days. A history of urethral strictures, posterior urethral valves, myelodysplasia with neurogenic bladder, and severe hypospadias with utricular enlargement may predispose to urinary tract infection, with secondary reflux into the ejaculatory ducts causing epididymitis (2). A history of scrotal pain and swelling associated with fever and parotid gland swelling suggest mumps orchitis.

Inguinal hernia and/or hydroceles may present with similar symptoms to acute testicular torsion. A history of constipation or upper respiratory infection, both causing increases in intraabdominal pressure may be present.

Henoch-Schonlein purpura, an uncommon cause of acute scrotal swelling (usually bilateral), is associated with a history of vasculitis and associated onset of a cutaneous purpuric scrotal rash (2).

Trauma, even minor, may be a cause of testicular pain and should be sought in the history (straddle injury, wrestling, sports). A history of trauma may suggest a traumatic etiology of pain and swelling, but this does not necessarily rule out the presence of testicular torsion.

The physical exam should be begun in conjunction with the history taking. The level of distress is noted along with vital signs and examination of the abdomen. There should be a specific notation of the presence or absence of inguinal and scrotal swelling, urethral discharge, scrotal or perineal ecchymoses or rashes, and lastly the appearance of the testes and area of pain and/or tenderness. The absence of a cremasteric reflex, in conjunction with testicular tenderness, is commonly associated with testicular torsion (5). This reflex is usually present in epididymitis. It is elicited by gently stroking the skin of the inner thigh: the presence of the cremasteric muscle results in movement of the testicle in the ipsilateral hemiscrotum.

Acute testicular torsion should be considered the leading diagnosis until it is ruled out. The acute onset of severe unilateral unrelenting pain, tenderness, high riding testicle, with absent cremasteric reflex and no change in pain in response to testicular elevation (Prehn's sign), highly suggest testicular torsion. In testicular torsion, the affected testicle may be more cephalad than normal and it may lie transversely (horizontally). A change in position is not seen in epididymitis or orchitis.

If one is able to palpate the testicle separate from the epididymis, one can distinguish between testicular torsion, epididymitis, and testicular appendage torsion. The affected testicle is exquisitely tender in testicular torsion, and the epididymis may not be palpable, but is also tender if palpable. In epididymitis/orchitis, the testicle itself is not tender, but the epididymis is palpable and tender. Epididymitis has a more gradual onset, with tenderness being present. A cremasteric reflex is usually present, and the pain may be relieved with testicular elevation. Fever, pyuria, and dysuria may be present.

A torsion of a testicular appendage may present in a fashion similar to that of acute testicular torsion. The tenderness may be well localized to the upper part of the testes and a characteristic "blue dot" sign in the skin of the scrotum may be applicable. This blue dot is due to venous congestion of the appendix testis of the torsed appendage.

Color Doppler ultrasound scanning has great utility in differentiating between the above diagnoses and ruling out testicular torsion (6). Absence of blood flow to the affected testicle is noted in testicular torsion, whereas increased blood flow is noted in

epididymitis/orchitis. Flow to the testicle will be present in appendage torsion. Of course, these findings should be combined with the signs and symptoms, and not taken in isolation. Testicular anatomy is also appreciated with ultrasound, helping to evaluate for testicular rupture, hematomas, and tumors.

Nuclear scintigraphy is not commonly used today in the evaluation of the acute scrotum. CBC and urinalysis are helpful in evaluating infectious etiologies, but waiting for these results should not delay a Doppler ultrasound study. A hernia or hydrocele or varicocele can be distinguished on exam.

Acute testicular torsion requires emergent scrotal exploration, detorsion of the affected testicle, with orchiectomy if testicular ischemia and necrosis persists, or testicular fixation if blood flow and testicular viability is restored with detorsion. In either case, the contralateral testicle should be explored and testicular fixation performed with permanent suture.

Epididymitis/orchitis can be treated with antibiotic and anti-inflammatory drugs. Occasionally "sepsis" may result from severe cases, requiring hospitalization with intravenous antibiotics. The majority can be treated with outpatient antibiotics. Activity should be limited.

Acute testicular appendage torsion may be observed, with analgesics/anti-inflammatories if the diagnosis is firm. No testicular fixation is necessary as these are not commonly associated with abnormalities of the attachments. If the diagnosis is in doubt, emergent scrotal exploration is indicated.

Trauma with rupture of the tunica albuginea of the testes requires exploration emergently, with debridement and repair. An isolated hematoma may be observed. Henoch-Schonlein purpuric scrotal swelling may be managed medically. Neonatal torsion may require exploration, if the diagnosis is made early enough, but unfortunately, the majority are diagnosed too late for testicle viability. Hernias and hydroceles should be repaired, emergently if incarcerated, electively if not.

The salvageability of a testicle within 6 hours of torsion is very good. Greater than 6 hours is more worrisome, but exploration should be performed to remove a necrotic testicle, even with a late presentation, as diminished fertility may result from leaving in an infarcted testicle (2). Epididymitis responds well to rest and antibiotic therapy. Any predisposing factors should be corrected.

Questions

1. What are the signs and symptoms that help to differentiate acute testicular torsion from epididymitis?
2. How is color Doppler ultrasound helpful in the differential diagnosis of acute scrotum?
3. What is the cremasteric Reflex? Prehn's sign? The blue dot sign? The bell clapper deformity?
4. What is the time frame most advantageous to restoring viability of a torsed testicle?
5. How is acute testicular torsion managed?
6. How is acute epididymitis managed?

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Answers to questions

1.	Acute testicular torsion	Epididymitis
Onset	Acute	More gradual
Fever	Absent	May be present
Cremasteric reflex	Absent	Usually present
Scrotal lie of testicle	Cephalad/transverse	Lower in scrotum
Prehn's sign	No change in pain	Decrease in pain
Pyuria	Absent	May be present
Dysuria	Absent	May be present

2. Blood flow to the testicles can be evaluated rapidly and the testicular anatomy can be assessed. Normal or increased blood flow is seen in epididymitis, while absent blood flow is indicative of torsion. Testicular rupture as in trauma, can also be identified.

3. Cremasteric reflex: Gently stroking the medial thigh elicits spermatic cord cremasteric muscle contraction and testicular movement. Prehn's sign: elevation of the affected testicle may improve the pain in epididymitis. Blue dot sign: a torsed ischemic testicular appendage may appear as a blue dot through the scrotal skin. Bell clapper deformity: incomplete investment of the tunica vaginalis onto the testicle and epididymis, with the testicle being predisposed to rotate, and torse, more easily than if the tunica vaginalis were present.

4. Detorsion within 6 hours of the onset of the torsion.
5. Acute scrotal exploration and testicular detorsion with bilateral testicular fixation (if the testicle was detorsed and salvageable).
6. Antibiotics for acute epididymitis.

Chapter XIII.11. Ambiguous Genitalia
Robert G. Carlile, MD

This is a term infant noted to have atypical genitalia with perineoscrotal hypospadias and a marked ventral chordee. This could be a penis or an enlarged clitoris. Gonads are nonpalpable bilaterally on examination of the labioscrotal folds. The parents aren't sure whether their child is male or female and this constitutes a neonatal (social) emergency. Further evaluation is commenced immediately. An ultrasound reveals a normal uterus and ovaries, as well as normal kidneys and bladder. Chromosomal analysis shows a 46XX karyotype. A genitogram reveals a short distal common urethrovaginal confluence, a vagina with a normal cervical impression, and a normal urethra.

At two weeks of age, this infant is admitted to the ICU with hypovolemic shock, and found to have hyponatremia and hyperkalemia. Plasma 17-hydroxy-progesterone levels are markedly elevated and plasma cortisol levels are low. Hydrocortisone and mineralocorticoid replacement are administered, along with intravenous fluids and electrolyte replacements, with a good response. She is diagnosed with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency.

A feminizing genitoplasty is performed at one year of age. This includes clitoral reduction and a flap vaginoplasty. In her mid-teens, the patient undergoes a vaginoplasty revision for introital stenosis.

Ambiguous genitalia are uncommon in a primary care pediatrician's practice, but their diagnosis and prompt treatment require urgent medical attention. Any delay may result in death in early infancy from an uncorrected metabolic disorder, if present. Quickly establishing a definitive diagnosis and appropriate treatment plan will minimize medical, social and psychological complications.

It is important to understand normal sexual differentiation in order to understand the development of intersex (ambiguous genitalia and sex determination) disorders. Up until six weeks of gestational age, the internal and external genitalia of the male and female fetuses are indistinguishable. The indifferent gonad is located on the urogenital ridge, with the Wolffian and Mullerian ducts nearby, which are destined to form the male and female internal ducts, respectively. The external genitalia in both sexes are represented by the genital tubercle, the urethral folds, and the labioscrotal swellings that surround the cloacal membrane (1). These primordial structures have the potential to produce either male or female genitalia.

The SRY gene, on the short arm of the Y chromosome, initiates male sexual differentiation (2). The SRY influences the undifferentiated gonad to form a testes, which produces the hormonal milieu that results in male sexual differentiation. Testosterone stimulates the Wolffian structures (epididymis, vas deferens, and seminal vesicles), and anti-Mullerian hormone suppresses the development of the Mullerian structures (fallopian tubes, uterus, and upper vagina). Testosterone converts to dihydrotestosterone in the skin of the external genitalia and masculinizes the external genital structures. By 12 weeks most of this male differentiation has occurred, after which the penis grows and the testes descend into the scrotum (3).

In the absence of these genetic (SRY gene) and hormonal influences (testosterone, anti-Mullerian hormone), the fetus will develop as a female. Intersex conditions arise because of an error along the male pathway that interferes with complete masculinization, or, in the case of a genetic female, some virilizing influence that acts on the developing embryo (3).

Infants whose genitalia are obviously indeterminate and ambiguous are investigated so that sex of rearing can be assigned. However, appearance can be deceptive. An apparent male may be a severely virilized female with congenital adrenal hyperplasia (CAH). An apparent female infant with only mild clitoral hypertrophy may be a male with severe androgen insensitivity.

Clinical findings in a newborn infant that raise the possibility of intersexuality (1,3) in an apparent male:

Bilateral nonpalpable testes in a full-term infant.

Hypospadias associated with clefting of the scrotal sacs.

Undescended testes with hypospadias.

Clinical findings in a newborn infant that raise the possibility of intersexuality (1,3) in an apparent female:

Clitoral hypertrophy.

Foreshortened vagina with single opening (instead of a urethral meatus and vaginal introitus noted separate from one another, there is just a single opening at the introitus and no separate urethral meatus visible).

Inguinal hernia containing a gonad.

Also, as noted above, those in whom the external genitalia are clearly ambiguous so that the sex cannot be immediately decided should be investigated.

A small number of children will only come to light in adolescence because of amenorrhea, inappropriate breast development, virilization, or the onset of cyclic "hematuria" (gross hematuria that occurs every 28 days, as a menstrual cycle would).

A careful history should be taken. An obstetric history should include any evidence of endocrine disturbance during pregnancy (mother with a Cushingoid or virilized appearance), and any medications taken during pregnancy (particularly any treatment for recurrent abortion or the use of hormonal contraceptives). As many intersex states are recessively inherited familial disorders, a family history may reveal genital anomalies, unexplained neonatal deaths, abnormal pubertal development, or infertility.

The physical exam starts with a search for evidence of a malformation syndrome. The genitalia are examined with the size of the phallus noted (a normal newborn stretched penile length should be greater than 2 cm and a normal clitoris is less than 7mm), and the position of the urethral meatus noted. Any penile chordee should be noted. The labioscrotal folds are evaluated for fullness, symmetry, rugosity and the presence or absence of a gonad (If a gonad is palpable in a female infant, then congenital adrenal hyperplasia is not present, as the CAH infant would have normal ovaries in the abdominal cavity). The position of the urethral meatus helps to determine the extent to which the urogenital sinus has closed (a separate urethral meatus and vaginal opening shows complete closure of the urogenital sinus while a single orifice suggests the persistence of a common urogenital sinus with the vagina and urethra connected distally). Areolar and labioscrotal hyperpigmentation associated with high levels of ACTH suggest congenital adrenal hyperplasia. The palpation of a uterus or cervix may be noted on rectal exam.

Since the appearances of the external genitalia vary so widely among patients who have the same condition, it is unwise to attempt a definitive diagnosis from the physical findings alone (1,3).

A chromosomal karyotype should be done in all patients. Since congenital adrenal hyperplasia is the most common cause of ambiguous genitalia in the newborn, serum 17-hydroxy-progesterone and deoxycorticosterone levels should be checked along with serum electrolytes and glucose in the infant with symmetrical masculinization and nonpalpable gonads (3,4).

A pelvic ultrasound will delineate the uterine anatomy, if present. It should normally be located posterior to the bladder. The kidneys and ureters should also be imaged. A genitogram will delineate the anatomy of the vagina, the uterine canal, one or two fallopian tubes, and/or the vasa deferentia, as well as the level at which the vagina enters into the urogenital sinus, if present (1,3). It is performed by injecting contrast retrograde through the common urogenital sinus (or the urethra and vagina if the urogenital sinus has closed), under fluoroscopy.

Further biochemical profiles may be necessary to identify a block in testosterone biosynthesis, decreased 5-alpha-reductase activity or androgen insensitivity (3).

Gonadal inspection and biopsy are necessary and can be done laparoscopically in many cases by an experienced pediatric urologist or pediatric surgeon. This will not be necessary in established cases of congenital adrenal hyperplasia and Turner syndrome. Cystovaginoscopy provides valuable information because it augments the genitogram's findings and aids in treatment planning.

The classification of intersex disorders are most conveniently divided into four main groups based on gonadal histology: 1) Female pseudohermaphrodites (two normal ovaries present). 2) Male pseudohermaphrodites (two normal testes present). 3) True hermaphrodites (both ovarian and testicular tissue are is found in the same patient). 4) Gonadal dysgenesis conditions (the gonads are histologically disordered; e.g., streak gonads) (1,3,5).

Female pseudohermaphrodism is a disorder in which a chromosomal female (46XX), with normal ovaries and mullerian derivatives and normal fertility potential, has virilized external genitalia (enlargement of the phallus and labioscrotal fusion are present to varying degrees). This virilization of the female fetus is secondary to androgens from either the maternal circulation or the fetal adrenal gland.

Congenital adrenal hyperplasia (CAH) is the most common cause of female pseudohermaphrodism, as well as the most common intersex disorder. The adrenal glands, in CAH, overproduce testosterone because an enzyme defect in intermediate metabolism results in decreased cortisol synthesis, which leads to an increase in circulating adrenocorticotropic hormone (ACTH), and thus to hyperstimulation of the adrenals (5). Because some forms of CAH are associated with salt-wasting, prompt monitoring and correction of electrolytes and corticosteroid/mineralocorticoid replacement are crucial. CAH is an autosomal recessive disorder that occurs in 1 of 15,000 births in the United States (6).

21-hydroxylase deficiency is the most common (95% of the cases) enzyme defect that causes CAH, with salt-losing a feature of a complete deficiency. 11-beta-hydroxylase deficiency is a rare form of CAH, which results in an accumulation of deoxycorticosterone, a potent mineralocorticoid. This results in salt retention and hypertension.

21-hydroxylase deficiency is suspected in a masculinized infant without palpable gonads and with Mullerian derivatives (female internal pelvic organs) evident on pelvic ultrasound. A 50 to 100 fold increase in serum 17-hydroxyprogesterone and a 46XX karyotype confirms the diagnosis. Salt wasting occurs in 75 percent of patients with classical disease, and is evident within the first two weeks of life, with resultant hyponatremia, hypokalemia, and inappropriate sodium wasting (high urine sodium despite hyponatremia) due to low serum aldosterone and elevated plasma renin activity (7). It is crucial to recognize this potentially life-threatening condition in the newborn period and institute replacement of cortisol and mineralocorticoid as necessary.

Other causes of female pseudohermaphrodism are maternal progesterone ingestion (with androgenic side effects) administered during pregnancy to prevent abortion, a virilizing ovarian or adrenal tumor in the mother, or idiopathic causes.

Male pseudohermaphrodism results from inadequate virilization of the male embryo. Chromosomal males (46XY) possess testes, but the male anatomic genital development is abnormal. Cellular testosterone sensitivity is abnormal in 80 percent of cases, and testosterone production is deficient in the remaining 20 percent. The causes include androgen insensitivity, gonadotropic failure, Leydig cell agenesis, bilateral vanishing testes syndrome, persistent mullerian duct syndrome, testosterone biosynthesis defects and 5-alpha-reductase deficiency (5).

Patients may have abnormal male genitalia, ambiguous genitalia, or female genitalia with palpable or nonpalpable testes, depending on the completeness and nature of the defect and the extent of gonadotropin oversecretion.

Androgen insensitivity is the most common (1 in 20,000 male births) cause of male pseudohermaphrodism and results from dysfunction or reduction of the androgen receptor. For complete testicular feminization, the androgen receptor is absent or completely nonfunctional. The pituitary and hypothalamus are insensitive to testosterone and thus secrete large amounts of gonadotropins, which results in the oversecretion of testosterone and estrogen (5). Breast development, general body habitus, and distribution of body fat are female in character. The clitoris is normal or small, and the vagina is short with a blind ending, but the external genitalia are female in appearance. All internal genitalia are absent (no uterus or ovaries) except for the gonads, which have the histologic appearance of undescended testes (6). Because of increased tumor risk in the undescended testes (5% to 10%), gonadectomy is recommended after puberty.

Patients with complete androgen insensitivity syndromes (testicular feminization) are normal phenotypic females who present during childhood with one or both testes palpable in an inguinal hernia, or with amenorrhea at puberty. A few are diagnosed based on discrepancy between prenatal karyotype and phenotype at birth (i.e., a 46XY karyotype with female external genitalia at birth). The diagnosis is based on clinical and family history, endocrine studies and, if indicated, androgen binding analysis in genital skin fibroblasts (5).

In the 17-beta-hydroxysteroid dehydrogenase deficiency (the most common biochemical defect causing deficient testosterone biosynthesis without CAH, which causes male pseudohermaphrodism), males have feminine external genitalia with mild to moderate degrees of clitoral hypertrophy, but with a separate urethra and blind ending vaginal pouch. Testes are usually inguinal. The diagnosis is often made at puberty, when progressive virilization associated with penile growth, attainment of male secondary sex characteristics, testicular descent, and a change in gender identity may occur (5).

5-alpha-reductase deficiency (pseudovaginal perineoscrotal hypospadias) is an autosomal recessive disorder associated with failure of dihydrotestosterone (DHT) formation, resulting in normal male internal Wolffian duct derivatives, but the external genitalia fail to virilize in utero (DHT is necessary for the external genitalia to masculinize while the internal genitalia masculinize in the presence of testosterone). The internal male genitalia are normal, and the testes are located in the labioscrotal pouch. The external genitalia typically show severe perineoscrotal hypospadias and a blind vaginal pouch opening into the urogenital sinus or urethra. At puberty, normal levels of luteinizing hormone and testosterone result in masculinization of the external genitalia, and breasts do not develop (5,6).

True hermaphrodism is a rare condition in which ovarian and testicular tissue exist in the same individual. 70 percent are 46XX (but they possess the SRY gene), 10% are 46XY, and the remainder show either mosaicism or chimerism (evidence of development from

two zygotes). Patients most commonly have ambiguous genitalia, but near-normal female and male genitalia may be present. A unicornuate or bicornuate uterus is usually present, and the differentiation of the genital ducts is determined by the ipsilateral gonad, with the ovary usually located on the left side (5). The most common gonad found is the ovotestes (50%), followed by ovary (30%) and testes (20%). Combinations are ovotestes/ovary (34%), bilateral ovotestes (27%), ovary and testes (27%) and ovotestes/testes (12%). The ovarian tissue is potentially fertile, but the testes are not (5).

A well masculinized patient may rarely present after puberty with gynecomastia, cyclical hematuria, or scrotal pain secondary to ruptured ovarian follicles.

In most patients, the external genitalia are masculinized to some extent, and two thirds of true hermaphrodites are raised as males. Of those raised as males, 80 percent have hypospadias and over 50 percent have labioscrotal fusion. Of those raised as females, two thirds will have clitoromegaly. All patients have a urogenital sinus, and in most cases, a uterus is present. The ovary is found in a normal location, but the testes or ovotestes may be at any point along the path of testicular descent (5). In addition to imaging studies, a gonadal biopsy is necessary to prove the existence of both ovarian and testicular tissue.

Dysgenetic gonads (histologically disordered gonads) are noted primarily in mixed gonadal dysgenesis, pure gonadal dysgenesis, and gonadal dysgenesis (Turner Syndrome). Mixed gonadal dysgenesis is the second most common intersex disorder. Karyotype is usually a mosaic 45XO/46XY. A testis is usually found intraabdominally opposite a streak gonad (resembling ovarian stroma histologically). A unicornuate (only one side of the uterus is present) uterus, fallopian tubes and vagina are present. The genitalia are ambiguous with severe hypospadias, a urogenital sinus, and labioscrotal fusion, with an undescended testicle. One third exhibit Turner stigmata (short stature, shield like chest, webbed neck, multiple pigmented nevi, and cubitus valgus) as well as cardiovascular and renal anomalies (5,6).

The incidence of gonadal tumors is 25 percent in patients with mixed gonadal dysgenesis and may arise in the streak gonad or the undescended testes. A gonadal tumor has not been described in a scrotal testes (8). Early bilateral gonadectomy with female rearing is appropriate in phenotypic females. In phenotypic males with a scrotal testes, male rearing is appropriate, but the streak gonads must be removed.

Pure gonadal dysgenesis is an abnormal differentiation of the gonads without a chromosomal abnormality. A 46XX female has normal immature female external genitalia, intact Mullerian duct structures and bilateral streak gonads. They have no stigmata of Turner syndrome. They usually present as adolescent females who fail to mature and reach menarche (5).

Patients with 46XY "pure gonadal dysgenesis" also have bilateral streak gonads, intact Mullerian structures, a female phenotype, and the absence of Turner stigmata. Some may present in the newborn period with clitoromegaly. These patients with the Y chromosome are at high risk for the development of gonadal tumors, so prophylactic gonadectomy is indicated (6,8).

Gonadal Dysgenesis (Turner Syndrome) is due to the loss of the second X chromosome (45XO), with resultant bilateral streak gonads, normal Mullerian duct development, and phenotypically female external genitalia. Mosaicism (45XO/46XX) lessens the severity of the gonadal abnormality. As neonates do not have ambiguous genitalia, the syndrome is usually diagnosed from investigations for other neonatal anomalies, which include: intrauterine growth retardation, head and facial anomalies, lymphatic anomalies, cardiovascular or urinary tract malformations or skeletal anomalies) (8). All should be raised as females, with gonadectomy indicated only in those with virilization or with clear evidence of a Y cell-line (6,8).

A child born with ambiguous genitalia constitutes a social and medical emergency. In the delivery room, no attempt should be made to suggest a diagnosis or assign a gender. The parents should be told that development is incomplete and further tests will reveal the appropriate gender. The infant should be referred to as "your baby" not "it", "he", or "she". Examination of the child in the presence of the parents to demonstrate the precise abnormalities of genital development is helpful, noting that the genitalia of both sexes develop from the same primordial structures, that both incomplete development or overdevelopment of the external genitalia can occur, and that the abnormal appearance can be corrected and the child raised as a boy or girl, as appropriate (3). A family should never be told that their child is male, but will be made female, or vice versa. Parents should be encouraged not to name the child or register the birth, if possible, until the sex of rearing is established. The parents need to be included in the discussions regarding sex of rearing decisions.

Transfer of the child to a tertiary care facility is usually necessary for optimal assessment and treatment. A multidisciplinary medical team, with representation from neonatology, endocrinology, urology, psychiatry and genetics services is useful. Pediatricians have a key role in coordinating the diagnostic evaluation, helping families understand their child's medical condition, and maintaining open communication between the family and other health care team members. The presence of the nursing staff is also critical at meetings, for it is they who will be spending the most time with the family and neonate.

The decision as to the appropriate sex of rearing of an infant, born with ambiguous genitalia, is based on the fertility potential, capacity for normal sexual function, endocrine function, potential for malignant change in a gonad, and psychosexual factors (testosterone imprinting) (3).

In female infants with CAH, exposure to maternal androgens, and rarely true hermaphrodites, can be expected to be potentially fertile and should be raised as females. The potential for fertility in most other intersex conditions is either reduced or absent.

Phallic size and its potential to develop at puberty into a sexually functional organ, are very important when male sex of rearing is considered. Testosterone injections may need to be given in equivocal cases, and the infant raised as male only when there is a very good response (especially in those with partial androgen insensitivity). The severity of the hypospadias should not be a deciding factor in the sex of rearing, as the results of hypospadias repair, using current techniques, are satisfactory, both functionally and cosmetically.

It is advantageous to retain a gonad appropriate to the assigned sex if it is likely to function adequately. The ovaries of virilized genetic females can be assumed to be normal. The ovaries of true hermaphrodites may also produce estrogen adequately. The testes of true hermaphrodites and those of infants with mixed gonadal dysgenesis may initially show good function, that later declines, so that testosterone supplements may be necessary from puberty onward (3).

There is potential for malignant degeneration in streak gonads, especially those with a Y-chromosome-bearing cell line. Testes that show dysgenetic features on biopsy should also be excised. Histologically, normal undescended testes have an increased incidence of tumor development, but can be preserved in a sex assigned male, with an orchiopexy, and the patient kept under long-term observation. Gonadectomy is considered when the risk of malignancy exists, or when gonadal tissue inappropriate to the assigned gender has been identified.

In the past, it was assumed that sexual identity was largely a result of rearing. However, in the past decade it has become apparent that testosterone imprinting of the fetal brain may play a role in determining male sexual orientation. Some girls with CAH engage in more typically male-like behavior patterns than their unaffected peers. Despite these findings, extreme caution should be exercised when a recommendation is made that the sex of the rearing should be different than the chromosomal sex (3).

Genital reconstruction is necessary in the majority of patients with ambiguous genitalia and intersex disorders once the multidisciplinary team, in conjunction with the family, have decided on the appropriate gender assignment.

Male reconstruction may require hypospadias repair (usually done between 6 months and 1 year of age), orchiopexy, and removal of inappropriate gonads as well as internal Mullerian structures.

Female reconstruction, also known as a feminizing genitoplasty, may involve a clitoral reduction and a vaginoplasty. Clitoral reduction can be done in a nerve sparing fashion, so as to preserve sensation and allow for orgasm, and is carried out as early in life as possible. Minor clitoromegaly can be left alone, as clitoral involution will take place once the source of androgen is shut down.

Vaginoplasty in a low lying vagina (flap-vaginoplasty) can be usually done at the time of clitoral reduction. This primarily widens the introitus. A major vaginal reconstruction for creation of a vagina de novo (substitution vaginoplasty) is best deferred until at least one year of age, or even until puberty.

Psychological and metabolic supports are also essential over time. Most individuals are able to function in the normal range and are well adjusted after treatment of intersex disorders. Certain affected individuals will have conflicts between their psychosexual orientation and their genital appearance and function. Thus, ongoing counseling of the parents and the affected child is advisable. Problems can be minimized when evaluation and treatment is done promptly by an appropriately constituted intersex team.

Questions

1. What clinical findings in an apparent newborn male raise the possibility of intersexuality?
2. What clinical findings in an apparent newborn female raise the possibility of intersexuality?
3. What findings in an apparent adolescent suggest the possibility of intersexuality?
4. What are the two most common causes of ambiguous genitalia in the newborn?
5. What laboratory and imaging studies should be done to investigate the infant with ambiguous genitalia?
6. What factors need to be weighed in deciding the appropriate sex of rearing for a newborn with ambiguous genitalia?
7. What genital reconstruction may be necessary in an infant with ambiguous genitalia and an assigned male sex of rearing? An assigned female sex of rearing?

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Answers to questions

1. Bilateral non-palpable testes in a full term infant. Hypospadias associated with separation of the scrotal sacs. Undescended testes with hypospadias.
2. Clitoral hypertrophy. Foreshortened vagina with single opening. Inguinal hernia containing a gonad.
3. Amenorrhea, inappropriate breast development, virilization, or the onset of "cyclic hematuria".
4. Congenital adrenal hyperplasia and mixed gonadal dysgenesis.
5. Chromosomal karyotype, pelvic ultrasound, genitogram, cystovaginoscopy, gonadal inspection and biopsy, and biochemical studies as necessary (i.e., in an infant with symmetrical masculinization and non-palpable gonads, serum 17-hydroxyprogesterone, deoxycorticosterone, electrolytes, and glucose would be checked because of suspected congenital adrenal hyperplasia).
6. Fertility potential, capacity for normal sexual function, endocrine function, potential for malignant change in a gonad, and psychosexual factors.
7. Male reconstruction may require hypospadias repair, orchiopexy, and removal of inappropriate gonads and internal Mullerian structures. Female reconstruction may require a feminizing genitoplasty (clitoral reduction and vaginoplasty), as well as the removal of inappropriate gonadal tissue.

Chapter XIII.12. Hypospadias
Robert G. Carlile, MD

This is a term male infant who is noted to have a ventral penile chordee with mid-penile shaft hypospadias. His testes are descended bilaterally. No circumcision is performed. He voids normally, and at 6 months of age undergoes repair of the hypospadias and chordee using the foreskin as a vascularized graft. Postoperatively he develops a urethrocutaneous fistula along the suture line. This is repaired 6 months later, and he subsequently has no problems.

Hypospadias occurs in 1 of 300 males in the United States, and is the most common congenital anomaly of the penis (1). "Hypospadias" refers to an abnormal penile configuration in which the urethral meatus is located on the ventral surface of the penis, proximal to the end of the glans, and anywhere from the ventral gland to the perineum. Epispadias refers to the condition in which the meatus is located on the dorsal surface of the penis.

Penile chordee (ventral bending of the penile shaft) is often associated with hypospadias, and may be due to tethering or dysplasia of the ventral penile shaft skin (2). A dorsal hood of incomplete prepuce may also be present.

There is no single known cause of hypospadias. Genetic factors exist, most likely based on a multifactorial mode of inheritance (3). Hypospadias is more common in first degree male relatives. Fathers of affected boys have an 8 percent incidence of hypospadias; and male siblings, 14 percent. Undescended testes and inguinal hernia occur in about 9 percent of children with hypospadias (1,3). Other anomalies do not occur with any significance in isolated hypospadias. This is related to the fact that both are under androgenic hormonal control during development. There is a significantly increased incidence of intersexuality when both conditions coexist (4), and a karyotype should be considered (5).

Since urethral development occurs under the influence of dihydrotestosterone (which is converted in peripheral tissue from testosterone by 5-alpha-reductase), the development of hypospadias can be related either to a reduction in 5-alpha-reductase activity, to a lack of testosterone production, or to failure of the local receptors to recognize the hormone (2).

Hypospadias should be classified based on the anatomical location of the urethral meatus after the chordee has been released: glanular (meatus is located on the glans), coronal, distal shaft, midshaft, penoscrotal, scrotal, or perineal. Associated chordee should be described in terms of severity (mild, moderate, or severe). This provides the most practical classification of hypospadias.

Anterior hypospadias (glanular and coronal types) account for 50% of all hypospadias. Middle hypospadias (distal, midshaft, and proximal penile types) account for 30% of hypospadias cases. Posterior hypospadias (penoscrotal, scrotal, and perineal types) account for 20% of cases (1).

An older classification system, not used by urologists anymore, but which you may encounter, describes hypospadias by degrees. First degree with the meatus between the glans and the distal shaft; second degree with the meatus between the midshaft and the proximal shaft; and the third degree with the meatus being penoscrotal, scrotal or perineal. The severity of chordee is not considered in this system (2).

The pediatrician will be the first physician to exam the genitalia after birth. The foreskin should be examined for completeness circumferentially. Thinned ventral foreskin (a "hooded" penis) is associated commonly with hypospadias. The meatal position should be noted if abnormal (glanular, penile, penoscrotal, scrotal, or perineal), as well as the presence or absence of penile chordee (mild, moderate or severe). The stretched penile length in the newborn is 3.5 cm normally (range 2.8 cm to 4.2 cm) (3), and should be noted if abnormal.

The gonads should be palpated and any cryptorchidism (undescended testes) noted. Any scrotal abnormalities should also be noted, such as a bifid scrotum (a deep cleft between the scrotal sacs) or penoscrotal transposition (the penis lying in or beneath the scrotum). There is an increased incidence of an intersex state (the expression of male and female physical and sexual characteristics within the same individual) in unilateral and bilateral cases of cryptorchidism with hypospadias, especially if the hypospadias is severe (4). Any inguinal hernia should be noted.

If hypospadias is present, a family history of hypospadias should be noted. Any history of maternal ingestion of hormonal medication during pregnancy should be noted. Other congenital anomalies should also be noted (e.g., anorectal anomalies), if present.

Upper urinary tract abnormalities have been reported to be more frequent in boys with hypospadias (3,5). However, routine screening with ultrasound, IVP, or cystograms is not justified because the incidence of defective upper tract anomalies is low. If other associated anomalies are present, with a known higher incidence of upper urinary tract abnormalities (e.g., anorectal malformation), then imaging screening studies are justified (5).

No circumcision should be done in the newborn with hypospadias or any other penile anomaly, as the foreskin may be necessary to create a neourethra, and/or provide penile shaft skin coverage.

If the gonads are nonpalpable and the hypospadias is proximal (penoscrotal or scrotal), then the risk of having an intersex state is high, and emergent urologic consultation is indicated, as well as observation for salt wasting congenital adrenal hyperplasia conditions (the most common cause of intersex states). For hypospadias, urological consultation or referral should be obtained during or shortly after the neonatal period.

The goals of corrective surgery for hypospadias are to provide the child with a normally appearing circumcised penis with the urethral meatus well placed at the tip of the glans. The child should be able to stand to void and have a straight penis when erect (2). This will allow both normal voiding as well as reproductive functionality of the penis after repair.

The hypospadias repair is best performed when the patient is between 6 and 18 months of age. At this age, babies are amnestic of the procedure, post operative management while the patients are still in diapers is easier and allows the procedure to be performed as outpatient surgery (1). The child's anesthetic risk is lower after 6 months of age if a good pediatric anesthesiologist is used.

There are over 200 named surgical procedures to correct hypospadias (1), but there are general concepts in the approach to hypospadias repair common to all. Ventral penile chordee must be corrected first, as the urethral meatus may move proximally as the penis is straightened. Next, the urethroplasty (urethral advancement) is performed to allow the placement of the neourethra well into the glans (to the glans tip). The neourethra is formed from either local skin flaps, or from foreskin flaps (the reason circumcision is not performed). A glanuloplasty to create a normal appearing rounded glans penis may also be performed, if necessary. Penile shaft skin coverage is then accomplished by bringing penile shaft skin, or foreskin flaps ventrally. A short, small caliber silastic urethral catheter that drains directly into the diaper may be used to direct the urine away from the repair, which is removed 7 to 14 days later.

Most hypospadias repairs can be done with a single stage repair. Sometimes a 2-stage repair is necessary, especially for very long urethral defects. The chordee is corrected first, and the prepuce spread along the ventral shaft. Six months later, the neourethra is completed in a second stage repair.

The most common complication seen after hypospadias surgery are fistulae, strictures and recurrent chordee, occurring approximately 10 percent of the time (1,2,5). A wait of at least 6 months is necessary to allow complete healing of the tissue, before the secondary surgery is performed.

Although parents are usually quite distraught when their child is born with hypospadias, the technique for hypospadias repair used by pediatric urologists today are very successful in transforming the hypospadiac penis to a normally appearing and functioning penis, and can be done while the child is still in infancy.

Questions

1. What is the incidence of hypospadias in newborn males in the United States?
2. Why is the presence of non-palpable gonads and hypospadias worrisome?
3. What are the anomalies most commonly associated with hypospadias?
4. What are the goals of hypospadias repair?
5. What are some common complications of hypospadias repairs?
6. Describe the possible locations for the hypospadiac urethral meatus.
7. How should chordee be described?

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Answers to questions

1. 1 in 300 newborn males.
2. Nonpalpable gonads and hypospadias (especially severe proximal hypospadias) is associated with an increased risk of the presence of an intersex state (about 27%) (4).
3. Cryptorchidism and inguinal hernias.
4. A normal appearing circumcised penis with the meatus at the glans tip. The erect penis should be straight.
5. Urethral fistula, urethral stricture and recurrent penile chordee.
6. Glanular, coronal, distal penile shaft, midshaft, penoscrotal, scrotal, perineal.
7. Mild, moderate, severe.

Chapter XIV.1. Pulmocardiac Resuscitation

Rodney B. Boychuk, MD
Alson S. Inaba, MD

Paramedics are transporting a 5 month old male infant with respiratory distress, when he tires and stops breathing. The patient is bag mask ventilated with CPR in progress. On arrival in the emergency department, the patient is apneic, asystolic, and pulseless. The infant has no IV access. After brief bag mask ventilation, the patient is intubated with a tracheal tube. A colorimetric carbon dioxide capnometer detector device confirms proper tracheal tube placement. Findings now include:

1) Airway/breathing: Breath sounds are equal bilaterally, and there is good chest movement with ventilation.

2) Circulation: No pulse is palpable without chest compressions, and no heart sounds are heard. ECG shows asystole. Oxygen saturation is not obtainable.

3) Vital signs: Heart rate 0, respiratory rate 0, blood pressure unobtainable.

4) Attempts at IV access are unsuccessful.

Ventilations and chest compressions are continued. Epinephrine 0.5 mg of the 1:1,000 solution is given down the tracheal tube, and an intraosseous line (IO) is inserted into the proximal left tibia. Blood is obtained from the IO needle and is sent for a number of studies including a rapid glucose check. The airway is reassessed, ventilation and chest compressions are continued, and a second dose of epinephrine is given. The patient converts to a sinus bradycardia with a fair blood pressure. After several more minutes of further stabilization, the infant's heart rate is 120 and he is beginning to move and cough against the tracheal tube. The resuscitation is a success.

Although the etiology of pulmocardiac resuscitation (PCR) in children is different than adults, the immediate goal is the same, to immediately reestablish effective cardiac output and tissue delivery of oxygen through the use of artificial ventilation, external chest compressions, and the administration of pharmacologic agents.

The pathophysiology of PCA (pulmocardiac arrest) in children is different from that in adults. The most common etiology of PCA in infants and children is respiratory failure with subsequent cardiac arrest; hence the term pulmocardiac arrest instead of cardiopulmonary arrest and PCR (pulmocardiac resuscitation) instead of CPR (cardiopulmonary resuscitation) as in adults. Furthermore, PCA in children generally is the end result of preceding progressive deterioration and rarely occurs as a sudden event. Thus it is vital to be able to identify and manage respiratory distress in children, and thus prevent the deterioration into respiratory failure and subsequent PCA.

There are many causes of PCA in children but most fit into the classifications of respiratory (pneumonia, apnea, bronchiolitis, asthma, submersion, aspiration, epiglottitis, smoke inhalation, suffocation, anaphylaxis), infectious (septic shock, meningitis), cardiovascular (congenital heart disease, arrhythmia, myocarditis, congestive heart failure, pericarditis, shock), traumatic, or central nervous system diseases (hemorrhage/edema, shaken baby syndrome, seizures, meningitis, hydrocephalus with shunt malfunction, tumor). Respiratory diseases and SIDS account for one-third to two-thirds of all pediatric PCA. Helpful history and physical exam items include: age, recent illness, previous medical problems, current medications, recent trauma, time of day, location of patient during PCA, access to toxins, medicines, poisons, access to potential foreign bodies, length of downtime, overall appearance (congenital defects, "special needs"), vital signs, tracheal deviation, subcutaneous air, pupillary response, evidence of trauma (including retinal hemorrhages), surgical scars (especially sternal, scalp which suggest surgical heart disease and brain surgery respectively). Findings which suggest prolonged time since death include rigor mortis, dependent lividity and corneal clouding.

The age distribution of childhood PCA is skewed toward infancy, with about 50% of patients younger than one year, about 25% between one and four years of age, and about 20% older than four years of age. Equipment and skills preparedness for this young age range by all EMS (emergency medical services) responders and those caring for pediatric emergencies is crucial for achieving best outcomes.

The outcome of PCA in children is dependent upon: 1) site of occurrence (i.e., in-hospital or out-of-hospital, and 2) cause of PCA. In eight reviews published since 1983, only 96/542 (17.7%) of children experiencing out-of-hospital PCAs survived versus 137/342 (40%) of those experiencing in-hospital PCA. The survival rates for children experiencing isolated respiratory arrests ranges from 75 to 97%, while survival rates for children experiencing full cardiopulmonary arrests range from 4 to 16%. The latter statistic reflects the terminal nature of asystole in children which is usually preceded by prolonged respiratory insufficiency with long-standing tissue hypoxemia and acidosis. Therefore directing initial management toward improvement of oxygenation and ventilation is imperative to a successfully resuscitation.

The initial approach to resuscitation is the same as it is for adults: A (airway), B (breathing), C (circulation), D (drugs). Attention to proper positioning, oxygenation and ventilation come first, with drug therapy last. Physiologically the ABC's can better be described as VOP (ventilation, oxygenation, and perfusion). In order to best accomplish this, an organized approach is necessary, with priorities established as follows:

1) Determine the level of responsiveness (or unresponsiveness).

2) Position the patient properly on a firm surface, maintaining cervical spine immobilization (in children with suspected head or cervical spine injury).

3) Establish a patent airway.

4) Assure oxygenation.

5) Assure or establish ventilation (breathing) while protecting the cervical spine.

6) Assure adequate circulation.

7) Reassess.

8) Utilize appropriate drug therapy if required.

The Broselow tape is a pediatric resuscitation tool which uses the length of the patient as a resuscitation guide providing intubation and drug dosing recommendations for each length along the tape corresponding to the patient's length. This eliminates the need to estimate the patient's age and weight.

The most common cause of upper airway obstruction in the unconscious child is posterior displacement of the tongue. This obstruction can be relieved by either a head tilt/chin lift or jaw-thrust maneuver, by pulling the jaw forward into a sniffing position. Do not perform the head tilt/chin lift maneuver in children with potential cervical spine trauma. Foreign material or vomitus can also obstruct the airway. Therefore open the mouth, inspect and suction early and repeatedly. Consider the use of nasopharyngeal or oropharyngeal

airways in selected patients. These type of airways should only be used in unconscious patients, because insertion of either a nasopharyngeal or oropharyngeal airway into a conscious patient will induce gagging and potential aspiration.

Assure oxygenation by administering supplemental oxygen. Although supplemental oxygen can be delivered to patients by a variety of different means, for the sickest patients, 100% oxygen should be administered, utilizing non-rebreather face masks at a flow rate of 10 liters per minute.

Children without adequate spontaneous breathing effort require positive pressure ventilatory support. Initially this is accomplished by bag mask ventilation. The American Heart Association Emergency Cardiac Care 2000 guidelines (1) refer to these the two bag mask ventilation devices as manual resuscitators which are: 1) the self-inflating bag and 2) the closed circuit anesthesia type bag (also called Rusch bag). The definitive airway, however, involves endotracheal intubation, which offers the most effective and secure means to deliver 100% oxygen and protect the airway. Tracheal tube (formerly called endotracheal tube) size should be determined according to one of the methods described in the intubation chapter, which also includes a description of the tracheal intubation procedure, placement and confirmation. The AHA ECC 2000 guidelines recommend secondary confirmation of proper tracheal tube placement by monitoring exhaled carbon dioxide using an end-tidal CO2 monitor or a colorimetric capnometer device (1). Adequate ventilation is determined by auscultation and chest movement (rise and fall).

Assuring adequate circulation does not mean just the blood pressure, but includes the evaluation of the overall appearance, heart rate, presence and strength of proximal vs. distal pulses, skin temperature and color, mucous membrane color, capillary refill time, alertness/responsiveness (brain perfusion) and blood pressure. With acute blood loss or any hypovolemic state, the protective/compensatory mechanisms of increasing the heart rate and increasing the systemic vascular resistance (poor perfusion with cool extremities) will maintain a child's SYSTOLIC blood pressure within a normal range in spite of losses as high as 30% of the child's circulating blood volume. Once these protective homeostatic mechanisms are no longer able to compensate for the hypovolemic state, the child's systolic blood pressure will then abruptly decompensate to a pressure that is now hypotensive for age.

If circulation is inadequate (i.e., absent or ineffectual pulses), then external cardiac chest compressions should be started. Optimally, these should be administered in a compression to ventilation ratio of 5:1. Current recommendations are that in infants, compressions be applied evenly over the midsternum (i.e., directly over the heart ventricles), utilizing the two thumbs on the chest with the hands encircling the chest technique. To avoid any liver trauma, compressions should not be applied over the lower third of the infant's sternum. For children (1-8 years of age), use the heel of one hand to compress the lower half of the sternum (with a compression to ventilation rate also equal to 5:1). For children over 8 years of age, the adult method of chest compressions should be utilized (heel of one hand over the lower half of the sternum with the other hand laid over the back of the first hand. The compression ventilation ratio is 15 compressions followed by 2 breaths) (1).

Vascular access must be established early. Even a small gauge IV can be used for resuscitation, which is better than no IV at all. Intraosseous (IO) infusion should be considered early, especially in the case of cardiac arrest, or decompensated shock. Although IO lines were previously recommended for children <6 years of age, there is no current age limit on the use of intraosseous infusion. The preferred site of IO placement is the proximal medial aspect of the tibia. Any intravenous preparation (medication or fluid) can be given intraosseously, and blood (if available) from the IO needle can be used for many laboratory tests.

After every step, reassess the patient. Pay attention to the VOP, physical exam (i.e., chest excursion, heart rate, skin color, perfusion, etc.) and to results of pulse oximetry or ancillary tests.

Drug therapy during resuscitation is reserved for those who do not respond adequately to the ABC's, and is the last line of therapy, NOT the first. While supplemental oxygen is typically utilized in all resuscitation scenarios, the majority of these resuscitations will not usually require a large number of medications. Drug doses are usually based on the patient's weight. The Broselow tape is an excellent tool to assist with this task. Some of the drugs utilized in pediatric resuscitation are noted here, but the entire list of resuscitation drugs is beyond the scope of this chapter. Epinephrine increases HR, contractility, and BP. Atropine increases HR in cases associated with increased vagal tone. Amiodarone and lidocaine (anti-arrhythmia agents) are used to convert ventricular fibrillation, pulseless ventricular tachycardia or ventricular tachycardia with a pulse. Amiodarone can also be used for certain atrial tachydysrhythmias. Dextrose reverses symptomatic hypoglycemia (which is an easily reversible cause lethargy, seizures and a potential element in shock and cardiac arrest). Sodium bicarbonate reverses the metabolic acidosis associated with most arrest situations; however, optimizing ventilation to reverse the respiratory component of an acidosis takes priority. Sodium bicarbonate is the treatment of choice for arrests due to cyclic antidepressant overdose (potentially lifesaving). Naloxone reverses cardiorespiratory and CNS opiate narcotic depression. Adenosine converts paroxysmal supraventricular tachycardia (PSVT). Dopamine improves BP. Dobutamine increases contractility.

There are also a number of drugs that can be given down the tracheal tube (TT) if vascular access cannot be established. The 4 medications which can be given via the TT can be remembered by the mnemonic "LANE" or "LEAN" which include lidocaine, atropine, naloxone and epinephrine. Epinephrine given down the TT is always given as "high dose" (i.e., 0.1mg/kg of the 1:1,000 solution).

The more common dysrhythmias that one may be confronted with during a pediatric resuscitation include bradycardia, asystole and pulseless electrical activity (PEA, formerly known as electromechanical dissociation or EMD). Ventricular fibrillation and ventricular tachycardia are not very common in children, but may be the presenting dysrhythmia in adolescent patients secondary to various drug overdoses. The key point in the treatment of PEA and asystole is to hunt for reversible causes. The mnemonic used to recall the reversible etiologies of asystole and PEA is "PATH", which stands for pneumothorax (tension), acidosis (severe), toxic ingestion, tamponade (cardiac), hypovolemia, hypoxia (severe), hyper/hypokalemia and hypothermia (so the mnemonic is actually PAT2H4). Although most of these can be ruled out by the history and clinical examination, the possibilities of hyper/hypokalemia and severe metabolic acidosis should also be quickly ruled out with a rapid bedside lab testing device which is much faster then sending a specimen to the lab. The most common cause of PEA in children is hypovolemia. Therefore a rapid fluid bolus (20 ml/kg of IV normal saline) should always be considered as a therapeutic option in a child with PEA who is not responding to epinephrine, CPR and adequate ventilation/oxygenation.

Although a complete discussion of all of the pediatric dysrhythmia algorithms is well beyond the scope of this textbook, a synopsis of the key treatment points for the various pediatric dysrhythmias is listed below:

Asystole and PEA: CPR, intubation, epinephrine and hunt for the cause.

Bradycardia: Assure adequate oxygenation and ventilation first then consider epinephrine, atropine and transcutaneous pacing.

Paroxysmal supraventricular tachycardia (hemodynamically stable): May attempt vagal maneuvers first, then consider adenosine.

Ventricular tachycardia (hemodynamically stable): Consider amiodarone or lidocaine or procainamide.

Any hemodynamically unstable tachydysrhythmia: Immediate synchronized cardioversion is the treatment of choice (unless vascular access is immediately available in the case of PSVT, in which case IV adenosine may be attempted first before cardioversion).

Ventricular fibrillation or pulseless ventricular tachycardia: Immediate defibrillation, epinephrine, intubation then consider antidysrhythmics such as amiodarone, lidocaine or magnesium sulfate (if torsades or hypomagnesemia).

Post resuscitation interventions include maintenance of normal ventilation (rather than hyperventilation), maintenance of normal temperature, glucose control, and management of post-ischemic myocardial dysfunction. Lastly, post arrest cardiogenic shock and septic shock must be treated aggressively with fluid, inotropes and pressors.

In summary, most seriously ill children experience respiratory distress followed by respiratory failure, or shock, before developing other organ system (i.e., cardiac) failure. Therefore a systematic approach to the early recognition and treatment of respiratory distress and compensated shock is the key to the prevention of pulmocardiac arrest. Oxygenation and ventilation must be established first. Without this, drugs, medication and resuscitation will be ineffective. The principles of ABC's (or VOP: ventilation, oxygenation and perfusion) must be followed by a trained skilled resuscitation team with proper equipment in a skilled facility.

Questions

1. The most common cause of pulmocardiac arrest in children is:
    a. Acute myocardial infarction
    b. Hemorrhagic shock
    c. Nonaccidental trauma
    d. Ventricular fibrillation
    e. Hypoxia and respiratory failure

2. Endotracheal intubation is not indicated for which of the following:
    a. Control and protection of the airway.
    b. Prolonged mechanical ventilation.
    c. Tension pneumothorax.
    d. Hyperventilation of the patient with a head injury.
    e. Improved oxygen delivery and ventilation.

3. The drug/treatment of choice for asystole in children is:
    a. Atropine
    b. Calcium chloride
    c. Adenosine
    d. Defibrillation
    e. Epinephrine

4. A 12 year old child comes to the ED pulseless. ECG reveals a wide complex tachycardia. Initial management should be:
    a. Immediate defibrillation.
    b. Immediate synchronized cardioversion.
    c. Adenosine
    d. Epinephrine

5. The most common cause of PEA in children is:
    a. Tension pneumothorax
    b. Metabolic acidosis
    c. Toxic ingestions
    d. Profound hypovolemia
    e. Hyperkalemia

6. The most common cause of bradycardia in children is:
    a. Hypokalemia
    b. Heart block
    c. Hypoxemia
    d. Toxic ingestions
    e. Myocarditis

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Answers to questions
1.e, 2.c, 3.e, 4.a, 5.d, 6.c

Chapter XIV.2. Shock
Rodney B. Boychuk, MD

This 2 month old male infant with a 4 day history of vomiting and diarrhea is brought to the emergency department by his mother. Initial findings in the emergency department include:

Airway: Breath sounds are normal. Airway is patent.

Breathing: Breathing is regular at 45 breaths per minute, unlabored.

Circulation: Proximal pulses are poor, distal pulses are absent, and extremities are cool. Feeling from the 5th toe upwards, the legs are cool up to the knee. Capillary refill is 8 seconds. Heart rate is 209 beats per minute, and blood pressure is 70mmHg systolic.

ECG: There are narrow QRS complexes with sinus tachycardia on the monitor.

The infant does not recognize his parents, is extremely lethargic, and responds to pain only, with a minimal grimace.

You are unable to start an IV line, 100% oxygen is started. The mucous membranes of the mouth are pink. An intraosseous (IO) is placed in the left tibia and 20cc/kg of normal saline is infused as rapidly as possible. The infant is reassessed. Airway and breathing remain stable. The heart rate is now 195. A repeat bolus of 20cc/kg is given and the patient is reassessed. After the 3rd fluid bolus is given, the patient becomes more alert, distal pulses return, and the patient improves throughout resuscitation. The heart rate has come down to 160. However, a rapid bedside glucose analysis reveals a blood sugar of only 32, which is quickly treated. This case represents a patient in compensated hypovolemic shock (and hypoglycemia) secondary to vomiting and diarrhea.

Shock is a clinical syndrome of circulatory dysfunction resulting in inadequate oxygen and nutrient delivery, with inability to meet the metabolic demands of the tissues (cells). This results in a cascade of events resulting in altered cellular metabolism, function, structure, and ultimately death. Shock is NOT necessarily hypotension. It begins with a normal blood pressure and progresses over time.

Normal circulatory function depends on 3 components: 1) adequate cardiac function (the pump), 2) appropriate vascular tone (the pipes) and 3) adequate blood volume (the fuel). When one of more of these circulatory components fail, shock results. Adequate delivery of oxygen and nutrients is dependent on adequate cardiac output (CO). Cardiac output in turn is dependent on two cardiac factors: 1) heart rate (HR) and 2) stroke volume (SV). As children are "heart rate dependent", the heart rate is the single most important vital sign when determining shock. The heart rate itself is regulated by two factors: 1) vagal tone and 2) catecholamines. Catecholamines are released in response to stress and have two major circulatory effects in children: 1) increase in heart rate (i.e., tachycardia), and 2) increase in peripheral vascular tone (resistance) (i.e., vasoconstriction, resulting in cool, clamped down extremities).

Stroke volume is the second determinant of cardiac output, and is dependent on three factors: 1) preload (intravascular volume/blood often called "venous return"), (the fuel), 2) myocardial contractility (heart muscle function), (the pump), and 3) afterload (systemic vascular resistance) (the pipes). Children are particularly dependent upon adequate intravascular volume, and when volume depleted, they peripherally vasoconstrict to maintain stroke volume. The myocardium in infants is "stiff" and plays little role in increasing cardiac output. Therefore, the heart rate must increase in order to maintain adequate circulatory function. Remember C.O.=H.R. x S.V.

Shock is a dynamic process that if untreated, progresses through three phases: 1) compensated, then 2) uncompensated, and finally 3) irreversible. Compensated shock, by definition, occurs in a body, which has successfully compensated to a circulatory disruption and is maintaining adequate vital organ perfusion and oxygenation. This may be difficult to differentiate from the patient's normal status. Blood pressure is normal. Tachycardia is usually present, and as catecholamine release increases, the heart rate increases and peripheral vasoconstriction with prolonged (delayed) capillary refill occurs. Utilizing my exam technique, "The pediatrician's handshake", I first feel the 5th toe. If the 5th toe is cold with a prolonged capillary refill, I progress to the other toes, up the foot, then the leg. The further up the leg the capillary refill is prolonged and the leg(s) is cool, the more vasoconstricted the body is, and when counted, the faster the heart rate will be. Normal capillary refill is 2 seconds or less, about the time I take to say "pepperoni pizza". If I need to add "more toppings" to my pizza, then I know the capillary refill is prolonged and the body is "in shock". There are pitfalls when interpreting capillary refill; if the body is developing a fever, or in a cold environment, vasoconstriction results and capillary refill is not a reliable sign of shock. Like any other single sign, this must be taken in context with all other findings.

As shock progresses (hopefully by now you will have intervened and are reversing and treating the cause and it will not progress), the compensatory mechanisms (i.e., increasing heart rate and vasoconstriction) reach their maximum ability and cannot increase further, then suddenly the body decompensates. Metabolic demands are not met, and cellular ischemia results in the release of vasoactive mediators which affect the microcirculation resulting in end-organ compromise and acidosis, with signs including hypotension, altered mentation, oliguria, acidosis, mottled pale skin with cool extremities, tachypnea and dyspnea, tachycardia and the obvious appearance of an "sick body". At this point irreversible damage of key organs (heart, brain, kidneys) may have occurred, but aggressive therapy is still indicated in chance that cardiovascular measurements can still be normalized. Unfortunately, despite aggressive therapy, death may occur regardless of therapy.

The main point to reemphasize is: the early recognition and treatment of compensated shock (better prognosis) is essential to prevent decompensated and irreversible shock (poor prognosis, high risk of death). Remember, hypotension is a late sign of shock and should not be allowed to occur.

Important historical information and physical exam findings must be included when considering the clinical manifestations and differential diagnosis of shock. Historical information asked must include: 1) age, 2) preexisting conditions/illness, 3) fever, 4) vomiting/diarrhea, 5) poor feeding, 6) urine output, 7) lethargy, 8) trauma, 9) toxic ingestion. The physical exam must include: 1) general appearance/alertness/eye contact/activity, 2) heart rate, 3) skin perfusion, a) capillary refill, b) color, c) skin temperature, 4) oliguria (if an observation period is permitted), 5) altered mental status, 6) tachypnea, 7) fever, 8) blood pressure, to name a few.

Utilizing history and physical exam information, it is important to classify the shock syndrome into one of 3 major etiologies: 1) hypovolemic shock, a) absolute, b) relative, 2) septic shock, or 3) cardiogenic shock. Hypovolemic shock is the most common cause of shock in children. A loss of circulating blood volume results in decreased preload (the fuel) with resultant decreased cardiac output. Absolute hypovolemia has three major causes; 1) dehydration secondary to a) diarrhea and vomiting or b) poor intake; 2) hemorrhage or 3) renal losses of fluid from a) diabetes mellitus or b) diabetes insipidus.

"Relative" hypovolemic shock is also called "distributive shock" where the problem is not related to absolute volume but to loss of vessel tone resulting in vasodilation and therefore a larger intravascular space (secondary to vasodilation) with a "normal blood volume", which results in a "relative" hypovolemia. There are four major causes of this: 1) sepsis, 2) anaphylaxis, 3) spinal cord injury or 4) drug reactions secondary to drugs such as barbiturates, phenothiazines, and antihypertensives.

Septic shock is a microcirculatory dysfunction that results from activation of a systemic inflammatory response from age-group specific bacterial pathogens. Those at risk for septic shock include: oncology patients, those with central venous (oncology) catheters, on chronic high dose steroids, or with a congenital or acquired immunodeficiency. Gram negative bacterial endotoxin-mediated septic shock results in activation of numerous mediators of circulatory failure. The end result is impaired myocardial contractility, alteration in vascular tone, and capillary leak.

Lastly, cardiogenic shock (the pump) may be the primary cause of shock or a late manifestation of other forms of shock. Here, there is an abnormality in cardiac function due to depressed myocardial contractility. Etiologies include 1) congenital heart disease, 2) myocardial infarction (e.g., Kawasaki's), 3) myocarditis or pericarditis, 4) congestive heart failure, 5) cardiac trauma, 6) dysrhythmia, or 7) drugs affecting myocardial contractility.

The table below compares the cardiac output (CO), systemic vascular resistance (SVR) and central venous pressure (CVP) in the three shock syndromes. An increase in CVP will clinically be seen as distended neck veins and an enlarged liver. An increase in SVR will be seen as cold, clamped down extremities with weak pulses and prolonged capillary refill.

	CO	SVR	CVP
Hypovolemic	decreased	increased	decreased
Cardiogenic	decreased	increased	increased
Distributive	increased	decreased	decreased

Common Etiologies of Shock Syndromes

1) Hypovolemic Shock

a) Absolute Hypovolemia: water and electrolyte losses (diarrhea, vomiting, diabetes insipidus, renal losses, heat stroke, intestinal obstruction, burns), hemorrhage (trauma, surgery, GI bleeding), plasma losses (burns, nephrotic syndrome, sepsis, intestinal obstruction, peritonitis).

b) Relative Hypovolemia (distributive shock): anaphylaxis (antibiotics, blood products, insects, vaccines, local anesthetics, foods, etc.), neurologic injury (head injury, spinal shock), drug intoxication (barbiturates, phenothiazines, tranquilizers, antihypertensives), sepsis., toxic shock

2) Septic Shock

a) Bacterial: Group A streptococcus, Haemophilus influenzae type b, Neisseria meningitidis, Streptococcus pneumoniae, Group B Streptococcus, Gram negative bacilli (predominantly E. coli), Staphylococcus aureus.

b) Other: viral, fungal, rickettsial

3) Cardiogenic Shock:

Congenital heart disease (ductal-dependent systemic blood flow, post-operative complications), dysrhythmias, drug intoxication, myocarditis (viral, other inflammatory), hypoxic-ischemic injury (Kawasaki syndrome, perinatal asphyxia, near-drowning, near-SIDS), primary cardiomyopathy, metabolic derangement (hypoglycemia, acidosis), hypothermia, late sepsis, toxic shock.

4) Miscellaneous Shock Syndromes

a) Obstructive Shock: pericardial tamponade, tension pneumothorax, pulmonary embolus

b) Dissociative Shock: carbon monoxide poisoning, methemoglobinemia

Regardless of etiology, initial therapy is universal. All patients should receive 100% supplemental oxygen by face mask, followed by the correction of the mismatch between metabolic supply and demand. Early recognition and aggressive treatment is the key. Anticipation of the effects of shock as a dynamic, clinical syndrome with multi-system consequences, which can be reversed, with optimization of cardiac output is essential to prevent decompensation and irreversible shock.

Treatment can be classified broadly into: 1) oxygenation, 2) vascular access, 3) fluid administration, and 4) drug therapy. Oxygenation includes providing 100% oxygen and also assuring adequate hemoglobin, stopping hemorrhage, and replacing blood if the hematocrit is less than 30%. Consider endotracheal intubation, but be aware of the cardiovascular effects that intubation and positive ventilation can cause, such as bradycardia, hypotension or reduced venous return. Vascular access includes insertion of a (preferably two) large intravenous catheters, and obtaining necessary lab tests (CBC, blood culture, electrolytes, BUN, creatinine, glucose, calcium,

coagulation profile and blood gas). If vascular access is difficult to obtain, use an intraosseous (IO) device and insert this into the tibia. New guidelines allow IO use in children of all ages. There are 2 major types of fluid that can be administered, crystalloid or colloid. Crystalloid is either volume expanding isotonic (normal saline or Ringer's lactate) or hypertonic (3% saline). Crystalloid is an effective volume expander in resuscitation but requires 2-4 times the volume of blood loss to restore hemodynamic parameters. Of the isotonic volume infused into the extracellular compartment (i.e., intravenous or I.O.), only 25% remains intravascular, while 75% eventually goes interstitial. This has led to the use of hypertonic saline (3% sodium chloride solution) in certain situations (such as hemorrhagic shock), as it is an effective vascular volume expander using less volume, working by expanding the ECF by a greater amount than the volume infused because it pulls water from the ICF compartment. Although there is less potential for edema as a result of its use, there are complications including increased serum osmolarity, increased serum Na and C1 levels, metabolic acidosis, and cerebral dehydration and hemorrhage.

Colloid refers to 5% albumin, fresh frozen plasma (FFP) or blood. Albumin's major advantage is that it remains primarily within the intravascular space (less enters the interstitial space). In addition, it can draw extravascular water into the intravascular space because of its oncotic pressure effect. FFP is an effective volume expander with the added benefit of procoagulant factors, while blood (whole or packed RBCs) is an effective volume expander with the added benefit of oxygen carrying capacity.

Most often fluid administration in the form of volume resuscitation is accomplished by the infusion of 0.9% sodium chloride (normal saline) or Ringer's lactate 20 ml/kg IV bolus as quickly as possible. Then reevaluate and repeat the bolus depending on the clinical status/changes. Search for other causes such as sepsis or occult hemorrhage. Central venous pressure monitoring will help fluid management in critical patients. General guidelines are to be liberal and aggressive with fluid resuscitation, giving 20 ml/kg initially and repeating as needed. For septic shock, more than 40ml/kg in the first hour has been shown to improve outcome. When approaching 80 ml/kg, consider the use of an inotropic agent such as dopamine or epinephrine.

Pharmacologic support includes medications that: 1) augment cardiac contractility (inotropic/cardiotonic), vasoconstrictors to reverse inappropriate vasodilation, and sometimes vasodilator drugs to reduce preload and afterload in cardiogenic etiologies, 2) antibiotics (for septic shock), 3) sodium bicarbonate, 4) calcium, 5) immunotherapies, and 6) controversial therapy. However, before specific drugs are described, a review of adrenergic receptor physiology is indicated. Each receptor has a different physiologic response, as noted here:

Alpha:	Arteriolar constriction
Beta-1:	Increased myocardial contractility (inotropy)
	Increased heart rate (chronotropy)
Beta-2:	Peripheral vasodilation
	Bronchial smooth muscle relaxation
Dopaminergic:	Smooth muscle relaxation
	Increase renal blood flow

Examples of classic agonists include phenylephrine (pure alpha), isoproterenol (pure beta, both beta-1 and beta-2), dobutamine (selective beta-1), albuterol (selective beta-2), epinephrine (both alpha and beta).

Three commonly used inotropic drugs include dopamine, dobutamine and epinephrine. Dopamine effects are dependent on the dose infused. Low dose (1-2 mcg/kg/min) results in vasodilation of the splanchnic (renal) and cerebral vascular beds. Mid-dose (3-10 mcg/kg/min) has primarily a beta effect (chronotropic and inotropic), while a higher dose (> 10 mcg/kg/min) has a pure alpha effect (pressor). Dobutamine has a pure beta-1 (chronotropic and inotropic) effect, the effective dose used ranging from 2-20 mcg/kg/min or greater. Epinephrine at an infusion dose of 0.05-2 mcg/kg/min has both beta and alpha effects, and may cause severe peripheral vasoconstriction or arrhythmias.

Examples of vasodilator drugs used for "afterload reduction" in a failing heart to ease the work of "pumping" are nitrates such as nitroprusside and nitroglycerine. Nitroprusside, infused continuously at a rate between 1-10 mcg/kg/min, is a vasodilator working on both resistance and capacitance sides of the circulation; however with time, a toxic cyanide metabolite is formed.

Consider the use of sodium bicarbonate after assuring adequate volume resuscitation and ventilation, at a dose of 1-2 mEq/kg.

Calcium: Hypocalcemia can occur after tissue hypoperfusion of any etiology and can result in myocardial depression and hypotension. If hypocalcemia is documented in a symptomatic patient not responding to inotropes and pressors, then consider treating the hypocalcemia. The dose used is 10-20 mg/kg CaCl (0.1-0.2 ml/kg of 10% solution). Monitor ionized calcium levels to determine its need.

Antibiotics are used for septic shock (or presumed septic shock). For ages less than 6 weeks, a combination of ampicillin plus cefotaxime can be used. For ages greater than 6 weeks cefotaxime or ceftriaxone can be used.

Immunotherapies include the use of anti-endotoxin (HA-1A or E5), anti-tumor necrosis factor (TNFa) and interleukin-1 (IL-1) receptor antagonist. These are beyond the scope of this chapter, but will be important adjuncts to antibiotics and intensive care treatment in the future. Controversial therapy includes primarily the use of steroids. Although theoretically it may be of benefit modulating the immune response to sepsis, there has been no benefit (actually increased mortality) in humans, therefore it is NOT currently recommended. A more detailed description of additional medications utilized for resuscitation can be found in the chapter on pediatric pulmocardiac resuscitation.

Ongoing assessment of the patient in shock includes repeated reassessments of the physical exam, and monitoring equipment including pulse oximetry, cardiorespiratory monitoring, repeated blood pressures, central venous pressure (if indicated), and urine output through a catheter. Physical exam findings will be reflected in signs of improved perfusion which will include improvement in appearance, including alertness (mental status), eye contact, skin capillary refill, color and temperature, heart rate and pulse strength, urine output, respiratory pattern and rate, and blood pressure. Resolving metabolic acidosis and declining serum lactate levels are lab findings indicating improvement of perfusion.

In summary, shock is a clinical syndrome NOT defined by blood pressure alone. Worldwide, hypovolemic shock from diarrhea represents the leading cause of death. Normal circulatory function depends on three factors: cardiac function (the pump), vascular tone (the pipes), and blood volume (the fuel). A disturbance in one or more, resulting in inadequate delivery of oxygen and nutrients to the tissues, leads to shock. Shock is a progressive, dynamic process where early recognition and immediate management (initially in the form of IV fluids) is essential to prevent deterioration into decompensated and finally irreversible shock.

Questions

1. Prioritize the initial management of the child with shock:
    a. Administer oxygen
    b. Administer volume resuscitation
    c. Support a patent airway
    d. Support blood pressure and perfusion with cardioactive drugs
    e. Administer antibiotics
    f. Address oxygen carrying capacity with administration of blood if anemia is present

2. The most sensitive indicator of intravascular volume in the pediatric patient is:
    a. Cardiac output
    b. Preload
    c. Heart rate
    d. Stroke volume

3. In the trauma patient with compensated shock, who is otherwise stable blood should be considered as part of volume resuscitation:
    a. Immediately after the airway is secured and intravenous access
    b. After 20 cc/kg of isotonic fluid has been administered without clinical response
    c. After 40 cc/kg of isotonic fluid has been administered without clinical response
    d. After 60 cc/kg of isotonic fluid has been administered without clinical response
    e. After isotonic fluid administration has resulted in inadequate clinical response and the patient requires operative repair

4. Which circulatory finding is the hallmark of the diagnosis of late (decompensated) shock?
    a. Capillary refill of 4 seconds
    b. Altered mental status
    c. Depressed anterior fontanelle
    d. Hypotension
    e. Absent distal pulses

5. An alert, 6 month old male has a history of vomiting and diarrhea. He appears pale and has an RR of 45 breaths per minute, HR of 180 beats per minute, and a systolic blood pressure of 85 mm Hg. His extremities are cool and mottled with a capillary refill time of 4 seconds. What would best describe his circulatory status?
    a. Normal circulatory status
    b. Early (compensated) shock caused by hypovolemia
    c. Early (compensated)shock caused by supraventricular tachycardia
    d. Late (decompensated) shock caused by hypovolemia
    e. Late (decompensated) shock caused by supraventricular tachycardia

6. Appropriate initial management for the child described in question 6 would include which of the following?
    a. Initiation of oral rehydration therapy
    b. Placement of an intraosseous line, fluid bolus of 20 ml/kg of normal saline
    c. Placement of an intravenous (IV) line, fluid bolus of 20 ml/kg of normal saline
    d. Placement of an IV line, adenosine 0.1 mg/kg IV

7. A 2 month old infant is brought to the ED with a pulse of 180 and BP 50/35 mm Hg. A liver edge is palpable to the umbilicus. Skin is mottled, capillary refill is 6 seconds with weak distal pulses. Chest x-ray reveals cardiomegaly. During the administration of 20 ml/kg of Ringer's lactate, respirations become labored and rales are heard. The next step would be:
    a. Sodium bicarbonate 1 mEq/kg IV
    b. Repeat fluid bolus 20 ml/kg
    c. Dopamine 5 to 10 mcg/kg/min IV infusion
    d. Synchronous cardioversion 0.5 joule/kg
    e. Epinephrine 0.01 mg/kg of the 1:10,000 solution IV

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Answers to questions

1. c,a,b,d,f,e
2. c
3. c
4. d
5. b
6. c
7. c. This represents a case of cardiomyopathy with four classic findings of congestive heart failure. Note that the patient's condition worsened with fluid administration. Dopamine would be the first agent to try. Epinephrine may be used later in desperation since its alpha effect may have detrimental consequences on overall circulation.

Chapter XIV.3. Respiratory Failure

Paula A. Vanderford, MD

A former 27 week premie, now 12 months old, arrives in the emergency room diaphoretic, cyanotic, and tachypneic, with a heart rate of 220. She has bronchopulmonary dysplasia (BPD), and is usually on home oxygen (30%) by tracheostomy collar. She is on routine albuterol and fluticasone aerosols for reactive airway disease. She has had cold symptoms for two days, slight fever and increased secretions. Today her parents report that she has had increased work in breathing with audible wheezing. Despite giving albuterol aerosols every two hours, she has worsened over the day. She "turned blue" about 30 minutes ago and an ambulance was called.

Exam: VS T 38.3, HR 220, R 90, BP 86/48, oxygen saturation 80% on an increased oxygen flow provided by paramedics. Her weight is 8 kg (25th percentile for a 9 month old, corrected post conception age). She has a tracheostomy tube in place. She is cyanotic and has poor aeration on auscultation. She has crackles, wheezing and a prolonged expiratory phase. Marked retractions and nasal flaring are present.

Suspecting a plug in her tracheostomy, her tracheostomy tube is suctioned and then changed when there is some resistance to passage of the suction catheter. Despite changing her tracheostomy, her status does not improve. She is bag ventilated via her tracheostomy and subsequently placed on mechanical ventilation. She is given IV methylprednisolone and more beta adrenergics. Her saturations rise from 80% to 98% and her aeration improves. Her tachycardia improves to 170 and her RR is now 50 (ventilator). She becomes more alert and her flaring and retractions subside. Her chest x-ray reveals chronic changes consistent with BPD, hyperaeration and scattered areas of atelectasis. Her nasopharyngeal RSV assay is positive for respiratory syncytial virus.

This is a case of respiratory failure due to RSV pneumonia in a patient with underlying BPD. In evaluating this child, multiple etiologies had to be considered, including problems with the tracheostomy. A plugged tracheostomy tube must always be considered as the cause of respiratory distress in a child with a tracheostomy.

There are multiple etiologies of respiratory distress, and the treatment obviously depends on the cause. Fortunately, the basic tenants of airway, breathing and circulation (the "ABCs") always apply. The goal is to recognize the early signs and symptoms of respiratory problems, intervene early, and hopefully prevent progression to respiratory failure.

What is respiratory failure? In the past, emphasis has been placed on arterial blood gas values. A more useful definition is based in clinical findings and history. Basically, respiratory failure is the inadequate ventilation and oxygenation, resulting in hypercarbia and hypoxemia severe enough to require ventilatory assistance. Evidence of respiratory failure includes cyanosis, tachypnea, apnea, slow respiratory rate, retractions, poor aeration, and appearance of fatigue. Depending on the etiology, the signs and symptoms will differ. Blood gases are useful if they are available and easily obtained. A blood gas obtained after multiple sticks in a dyspneic screaming, poorly perfused child may result in worsening of the child's status and provide little, if any, useful information. In the best of situations, an arterial blood gas (ABG) in a previously healthy child with a $PaCO_2 > 55$, $PaO_2 < 60$ is consistent with respiratory failure in most instances. She exhibited another common feature of respiratory failure, which is that she failed to adequately oxygenate despite maximal supplemental oxygen by mask. This can be easily assessed by monitoring the pulse oximeter readings while maximal supplemental oxygen by mask is administered. Note that in our case, the diagnosis of respiratory failure was made without obtaining a blood gas. Rather, respiratory failure was based on clinical findings alone. A blood gas might have delayed treatment and would not have changed the therapy. Given her BPD, we would expect her pCO_2 to be high at baseline, but with a fairly normal pH. In the setting of acute respiratory failure, a low pH is important in making this diagnosis in a child with chronically elevated pCO_2. Eventually in the therapy of a child with respiratory failure, blood gases will be helpful in managing therapy. Well warmed capillary blood gases are useful in following pH and pCO_2 in a child with good perfusion (as an alternative to ABGs). Oxygen saturation measured by pulse oximetry and end tidal CO_2 monitoring ($ETCO_2$) or transcutaneous CO_2 monitoring (TCM) are also useful for monitoring during therapy.

There are many etiologies of respiratory failure including neurologic disorders, respiratory infections and foreign bodies. Some specific conditions include: head injury, coma, status epilepticus, narcotics/sedatives, botulism, Guillain-Barre syndrome, airway foreign body, croup, asthma, tracheomalacia/tracheal stenosis, flail chest, burns, bronchiolitis, pneumothorax, pleural effusion, pneumonia, ARDS/neonatal RDS, pulmonary edema, etc.

While the specific treatment depends on the etiology, assessing and supporting the ABCs is the appropriate initial therapy. Managing the airway, supplying oxygen and assuring adequate ventilation are the goals regardless of the etiology. Specific treatments, however, depend on determining the location and cause of the respiratory distress. Chapters in multiple books have been written about each specific disorder. Given the limited scope of this chapter, only a few of the more common disorders will be described and their therapies outlined.

If there is evidence of upper airway obstruction, such as snoring or harsh stridor, repositioning the airway may be useful. Suctioning the naso/oropharynx may be helpful, and in certain cases airway adjuncts such as an oral airway or nasopharyngeal tube may be necessary. Upper airway problems are generally manifested by stridor and include epiglottitis, croup, laryngomalacia, vocal cord problems and airway foreign bodies.

Epiglottitis has become much less common since the wide spread use of the Haemophilus influenza B vaccine. Epiglottitis is characterized by high fever, a toxic appearance, drooling and a muffled voice. Therapy includes oxygen, endotracheal intubation and antibiotics.

Croup is much more common, occurs predominately in infants, and is characterized by a barking or seal-like cough, stridor and low grade temperature. Therapy includes oxygen, epinephrine aerosols and corticosteroids. Only rarely is endotracheal intubation necessary.

Laryngomalacia, vocal cord problems and foreign body aspiration are generally diagnosed by history and laryngoscopy/bronchoscopy. Oxygen is always an appropriate initial therapy, offered in the least threatening manner. Intubation may be required acutely for severe laryngomalacia and vocal cord dysfunction. Tracheostomy may be necessary for long term problems.

Foreign body aspiration should be suspected in a previously healthy child with the acute onset of respiratory distress. Frequently, unilateral wheezing or unequal breath sounds will be noted, along with unilateral findings on CXR (atelectasis or hyperaeration). Bronchoscopy and removal of the foreign body are usually the only therapy required for aspirated objects. In some cases where bronchospasm and airway swelling accompany the aspiration, bronchodilators, epinephrine aerosols and corticosteroids may be indicated.

Neurologic conditions that lead to respiratory failure, in contrast to airway or pulmonary problems, are not usually associated with signs/symptoms of respiratory distress. Respirations may be shallow, irregular or absent. Level of consciousness may be impaired, depending on the cause, but this may be difficult to assess due to muscle weakness. If the etiology is a sedative or narcotic overdose, oxygen and a reversal agent such as naloxone or flumazenil may be all that is necessary. For longer term conditions such as Guillain-Barre or botulism, intubation and mechanical ventilation are usually required until the neurologic problem resolves. Central hypoventilation and spinal cord injuries frequently result in the need for tracheostomy and long term ventilation.

Reactive airway disease, characterized by distal airway swelling, increased secretions and airway constriction is a common cause of respiratory distress/failure. Children with bronchiolitis, bronchopulmonary dysplasia (BPD) and asthma all have a component of reactive airways disease. Bronchiolitis is a viral illness, most commonly seen in infants. Oxygen is always indicated for the child in distress. Bronchodilators may be helpful. Corticosteroids are most helpful in those with a prior history of reactive airways disease. Children with a history of prematurity and prior long term mechanical ventilation will often develop BPD with scarring of the lung and hyperactive airways. BPD exacerbations are characterized by hyperaeration and wheezing, and are often initiated by URIs. Frequently they will be on chronic bronchodilators and nebulized corticosteroids or steroid inhalers. It is important to ask this history since children on corticosteroids recently may be adrenal suppressed and require stress dose (high dose) corticosteroids with acute illnesses. Corticosteroids will also be useful in treating acute airway inflammation. More frequent bronchodilators (or continuous bronchodilators) may be helpful. The use of heliox and magnesium have been reported to be useful in some patients, but are not yet considered standard therapies. Helium/oxygen mixtures have a lower density than nitrogen/oxygen (room air) mixtures and therefore flow with less turbulence. Magnesium is a smooth muscle relaxant and has been reported to be useful for severe asthma by some investigators.

Pneumonia reduces lung compliance and increases ventilation perfusion (V/Q) mismatching due to lung injury and filling of the alveoli. Areas of atelectasis are also common due to mucus plugging. The patient with pneumonia may have grunting respirations (closing the glottis prematurely in order increase their intrinsic airway distending pressure to keep the alveoli open: PEEP), in addition to hypoxemia, tachypnea, rales, retractions, and nasal flaring. Treatment of the child with pneumonia and respiratory failure may include oxygen, antibiotics (if a bacterial process is thought to be present), chest physiotherapy to help open atelectatic areas and promote drainage, and mechanical ventilation. The provision of PEEP (positive end expiratory pressure) improves V/Q matching by improving ventilation of the involved alveoli. In some patients, continuous positive airway pressure (CPAP) alone will be sufficient to adequately restore ventilation and oxygenation, but in most cases, provision of mechanical ventilation will be necessary.

Adult respiratory distress syndrome (ARDS) is a disorder characterized by diffuse lung injury, bilateral infiltrates and a large alveolar arterial oxygen gradient (hypoxemia despite high inspired supplemental oxygen) resulting in significant hypoxemia. There are numerous etiologies for ARDS, including pneumonia, near drownings, sepsis and burns. The disease involves alveolar filling as well as interstitial edema and infiltration with cells and fibrosis. The prognosis is poor even with intensive care. Treatment includes tracheal intubation and ventilation, usually with "permissive hypercapnia" techniques to reduce barotrauma. Patients with ARDS have very stiff noncompliant lungs and using tidal volumes and rates sufficient to normalize the pCO2 often result in air leak complications (such as pneumothorax). Therefore, a high pCO2 (50s to 60s) is permitted, as long as the pH remains acceptable (variable, depending on the center). Morbidity and mortality have been shown to be reduced in patients with ARDS with this technique. Due to reduced lung compliance and alveolar filling, high PEEP is generally required to maintain oxygenation in patients with ARDS. High frequency oscillation ventilation is also frequently used. Air leaks are a common complication.

Air leaks are another cause/contribution to respiratory failure. A discussion of air leak syndromes is found in a separate chapter in this book.

This chapter provides only a brief overview of respiratory failure; its causes, signs and symptoms, and approaches to treatment. Early recognition of respiratory distress and intervention will help prevent progression to respiratory failure and eventual cardiopulmonary arrest.

Questions

1. True/False: To diagnose respiratory failure one must obtain an ABG.

2. Etiologies of respiratory failure include:
   a. burns
   b. botulism
   c. asthma
   d. pneumonia
   e. c & d
   f. all of the above

3. Upper airway problems are generally manifest by:
    a. wheezing
    b. grunting respirations
    c. stridor
    d. tracheal deviation

4. A previously healthy child with acute onset of respiratory distress and unilateral wheezing should be suspected of having:
    a. reactive airway disease
    b. croup
    c. foreign body
    d. epiglottitis

5. Children with a neurologic conditions resulting in respiratory failure often display:
    a. retractions
    b. rapid abdominal breathing
    c. head bobbing
    d. none of the above

6. Reactive airway disease is characterized by:
    a. distal airway swelling
    b. increased secretions
    c. airway constriction
    d. wheezing
    e. all of the above

7. True/False: Respiratory distress in a child with a tracheostomy should be considered a plugged or misplaced tracheostomy tube, until proven otherwise.

8. ARDS is characterized by:
    a. large alveolar-arterial gradient
    b. reduced compliance
    c. low morbidity & mortality
    d. a & b

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Answers to questions

1.false, 2.f, 3.c, 4.c, 5.d, 6.e, 7.true, 8.d

Chapter XIV.4. Intubation
Paula A. Vanderford, MD

This is a four month old male who presents to the ED with respiratory distress. His mother states that he has been ill for several days with a runny nose, fever and a cough. Last night she noted that he was breathing "funny". This morning he refused his bottle and has had increased difficulty breathing. He has had an episode of vomiting with cough, but no diarrhea.

His past medical history is significant for a home birth and no immunizations. He has been well since birth, with the exception of noisy breathing especially when he is in the supine position.

Exam: VS T 39.0, P 80, R 16, oxygen saturation 82% on RA, 90% on oxygen by mask, weight 6kg (50%ile), length 59cm (10%ile). He is in moderately severe respiratory distress with nasal flaring and marked chest retractions. He has unusual facies and a small jaw. His tongue is protruding from his mouth. He has a slightly sunken fontanel. His heart rate is rapid, but regular and no murmurs are noted. His breath sounds are equal but diminished. Crackles and diffuse wheezes are present bilaterally. His abdomen is full, but soft and his abdomen expands with each breath. His capillary refill time is 3 seconds. His pulses are 2+ to 4+ peripherally. His muscle tone is poor. Arterial blood gas (ABG) pH 7.12, pCO2 100, pO2 60, base excess -4. Chest x-ray shows diffuse bilateral patchy infiltrates, with hyperinflation and areas of atelectasis.

The child is correctly assessed to be in respiratory failure and he is sedated and pharmacologically paralyzed for intubation. Unfortunately, as the neuromuscular relaxant is given, the child becomes blue and bradycardic despite bag mask ventilation. The mask is repositioned and a good seal is obtained. However, there is poor chest wall movement with bagging. The child has upper airway obstruction and a nasal trumpet is placed. He is again bag mask ventilated and his saturations rise to 100%. Attempts to intubate the child are unsuccessful. His vocal cords cannot be visualized due to his relatively large tongue and small jaw. He is successfully bag mask ventilated until an anesthesiologist on call arrives and is able to intubate the child's trachea, using advanced techniques. He is placed on mechanical ventilation. His RSV assay is positive. He requires mechanical ventilation for approximately one week and is successfully extubated. During his hospital stay he is evaluated by a geneticist who confirms a diagnosis of Pierre Robin syndrome.

There are multiple indications for endotracheal intubation. These include respiratory failure secondary to lung disease, upper airway obstruction, CNS disease (such as increased ICP or apnea) or chest wall problems. Whatever the indication, endotracheal intubation should be carried out in a systematic, controlled fashion. This requires preparation before a patient in need arrives in your facility. Equipment must be available, appropriate to all sizes of children and adults, since many teenagers will require adult sized equipment. Equipment must be stored in an organized fashion and readily available. It should be checked frequently to assure that it is in good working order, especially the light source for the laryngoscope blade. Equipment should include: laryngoscope blades and handles, extra lights/batteries, endotracheal (ET) tubes (cuffed and uncuffed, all sizes), suction catheters, ventilation bag/masks in all sizes, oral and nasal airways, ET tube (ETT) stylets, Magill forceps, NG tubes, and tape. It should be noted that the term endotracheal tube (ETT), has recently been replaced by the term "tracheal tube" (TT). This chapter will use these two terms synonymously.

A croupy cough or stridor should alert the clinician of possible airway narrowing and a smaller than usual ETT should be available. The child's airway should be assessed, paying particular attention to any unusual anatomy that may prevent adequate visualization and successful endotracheal intubation. These include a small mandible, large tongue and a restricted mobility of the mandible. Obtaining a history of prior intubations is also important. A history of a difficult intubation should raise concerns regarding a potentially difficult airway and assistance should be sought from an anesthesiologist.

Once it has been determined that the patient requires endotracheal intubation, a decision must be made as to what, if any drugs will be used to facilitate the procedure. While newborns are commonly intubated without the use of any sedatives or neuromuscular relaxants, it is common practice in pediatrics to sedate and pharmacologically paralyze children for endotracheal intubation. Sedatives and/or analgesics and paralyzing agents make the procedure more comfortable for the patient and help blunt some of the hemodynamic responses to intubation. Neuromuscular relaxants make the procedure easier, as the tissues are relaxed, facilitating visualization and intubation. A description of all the agents used is beyond the scope of this chapter; however, midazolam, propofol, etomidate, ketamine, opiate narcotic analgesics, thiopental, rocuronium and succinylcholine are commonly used. The clinician must be aware of the potential side effects of each medication and their duration of action. As a general rule, long acting neuromuscular relaxants and arguably any neuromuscular relaxant should be avoided in a child with a potentially difficult airway. Pharmacologic paralysis could make a bad situation worse if endotracheal intubation is unsuccessful, as in the case presented. An anticholinergic, such as atropine may be given prophylactically to prevent bradycardia due to an exaggerated vagal response to intubation.

ETT size selection is critical to optimally ventilate a patient. One very easy guideline to remember is to use the size is the outer diameter of the 5th finger which should approximate the size of the outer diameter of the ETT. This rule sounds attractive, but it is difficult to use accurately in an emergency. Term newborns require a 3.0 or 3.5 ETT. 12 month olds generally fit a 4.0 ETT. For children over 2 years of age, the correct ETT size can be estimated by the formula: 4 + age/4

Uncuffed ETTs are used in children less than 8 years old. This is because the narrowest portion of a child's larynx is the cricoid, versus the glottis in adults. An ET tube a half size smaller and larger than the estimated needed size should be available. Straight blades (e.g., Miller) are most useful in infants and young children. The tip of the blade is used to lift (compress) the base of the tongue; however, often the blade is inserted farther and the tip of the epiglottis is lifted. For older children curved (e.g., Macintosh) blades are generally used to lift the tongue and expose the epiglottis and laryngeal opening. The size of the blade depends on the size of the child: Blade size 0 (newborns), size 1 (infant and small children), size 2 (older children), size 3 (adolescents and adults).

Once all the equipment has been assembled and checked, and medications are drawn up and available, the child is positioned supine in the "sniffing" position (the head is slightly extended with the jaw thrusting upward). Depending on the age of the child, a folded towel under the head may facilitate endotracheal intubation. This is generally not needed in infants due to the prominence of their occipital region. Placement of the head in this position allows for easier visualization of the epiglottis and vocal cords. If, however, the child is suspected of having a cervical spine injury, the neck should be stabilized in neutral position during endotracheal intubation. Ideally the child will have been NPO for several hours prior to intubation to avoid emesis and aspiration. If not, place a NG tube and aspirate the stomach contents. An NG tube is also useful to prevent insufflation of the stomach with air during preoxygenation and bag mask ventilation. If the child has not been NPO, "rapid sequence intubation" should be performed which minimizes bag mask ventilation and reduces the risk of aspiration (1). With the left hand, the blade of the laryngoscope is placed in the right corner of the mouth and the tongue is swept superiorly and to the midline. Avoid using the blade as a lever, instead lift up and away from you. Slowly pull back on

the laryngoscope blade until the vocal cords are visualized. Use your right hand to suction the oropharynx if needed, then use your right hand to pass the ETT between the cords. Do not force the tube if it does not pass easily. Stop the attempt if the child becomes bradycardic or if the saturations begin to fall, and resume bag mask ventilation. Once the ETT has passed between the cords, advance it until the "oral" mark on the ETT is at the level of the lip. As a rough guide, the lip to tip distance is 3 times the ETT size. A stylet may be used to facilitate intubation if there is difficulty placing the ETT anteriorly. Auscultate for breath sounds bilaterally and look for condensation in the ETT. If breath sounds are present on the right, but not the left, suspect a right mainstem intubation and slowly pull back on the ETT until breath sounds are heard bilaterally. Auscultate over the stomach as well, to rule out an esophageal intubation. End tidal CO2 monitors and detectors are the best means of confirming tracheal intubation in most instances. Then secure the ETT to both the upper and lower lip using an adhesive (such as benzoin) and tape. Appropriate respiratory support should be initiated immediately. A CXR should be obtained immediately to confirm proper positioning of the ETT. Remember that an intubated child is at risk for the displacement of the ETT, ETT plugging, pneumothorax or an equipment failure (ventilator malfunction). Assume that any deterioration in the child's status is an airway problem until that is ruled out as a cause. "DOPE" is a useful mnemonic to remember potential causes of airway/ventilation problems in intubated patients.

D: Displaced ETT
O: Obstructed ETT
P: Pneumothorax
E: Equipment failure (such as ventilator malfunction or disconnect)

Questions

1. True/False: Neuromuscular relaxants should always be used for endotracheal intubation.

2. The appropriate ETT size for a 4 y.o. is: a) 5.0 b) 4.0 c) 6.5

3. True/False: A cuffed ETT is appropriate for a 5 year old in respiratory failure.

4. True/False: Bag mask ventilation should be used to ventilate a child with dysmorphic features until an anesthesiologist is available for endotracheal intubation.

5. True/False: For infants, a Macintosh blade is the most useful for endotracheal intubation.

6. In an intubated patient the most likely cause of acute deterioration is:
   a. shock
   b. airway problems
   c. need for chest physiotherapy

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Answers to questions

1. false, 2.a, 3.false, 4.true, 5.false, 6.b

Chapter XIV.5. Mechanical Ventilation
Paula A. Vanderford, MD

A 4 month old, 6 kg girl is admitted to the PICU for respiratory failure. She is cyanotic and retracting. She is intubated due to worsening tachypnea, increasing work of breathing, and fatigue. Her oxygen saturations have been falling and her pCO2 is 75 on an arterial blood gas. With intubation, her oxygen saturations briefly improve as she is hand ventilated, but her oxygen saturation falls into the high 80s when placed on mechanical ventilation, SIMV (synchronized intermittent mandatory ventilation) mode with a tidal volume of 80, IT=0.7 seconds, FiO2=100%, PEEP=5, and rate of 25. Her saturations again rise to 98-100% with hand bagging. After numerous attempts to ventilate her with volume ventilation she is changed to SIMV pressure control/pressure support mode, PIP=30, PEEP=6, FiO2=60%, RR=25, IT=0.7 and her saturations remain 98-100% on mechanical ventilation. CXR shows her ET tube to be in good position, but there are bilateral, patchy infiltrates and right lower lobe consolidation. She is placed on chest physiotherapy and IV antibiotics. Over the subsequent week, her ventilator rate, FiO2 and PEEP are gradually reduced. She is successfully extubated one week after admission to the PICU.

Mechanical ventilation is an art that remains in flux. While there are some basic tenants, each child and disease process have different characteristics. Therefore, the mode of ventilation chosen must be evaluated to be sure it is optimal for the child and their illness.

The two commonly used ventilation modes are pressure and volume, with many variations depending on the ventilator. The modes are based upon what variables cause the ventilator to cycle from inspiration to exhalation. These variables include time, flow rate, pressure, and volume. Air/oxygen is delivered to the patient under positive pressure until a certain volume is delivered, a certain pressure is achieved, or time/flow criteria are met. The ventilator then diverts flow and allows the patient to passively exhale. The positive end expiratory pressure (PEEP; which is the pressure which is maintained using flow resistance, during exhalation), is also set, depending on the child's underlying illness. The ventilator stops diversion of flow when this pressure is achieved and maintains the end expiratory pressure until the next positive pressure breath is initiated.

There are pros and cons to each type of ventilation and advocates for each. It is known that mechanical ventilation may cause lung damage either due to "volutrauma" (trauma due to rapid, repetitive changes in lung volume) and/or "barotrauma" (trauma due to rapid, repetitive changes in lung pressure). The repetitive expansion and collapse of the lung can cause parenchymal injury and may alter lung water and mucociliary clearance. Which mode of ventilation is superior (if there is a "best" mode) depends upon the patient and their disease process. The basic difference between the ventilator methods, is the parameter used to end the inspiration cycle (pressure or volume). In pressure controlled ventilation, a PIP (peak inspiratory pressure) and an inspiratory time (IT) duration determines the inspiratory cycle. The advantage of a pressure ventilator is that it should help protect the lungs from excessive pressures. However, tidal volume (TV) may then be compromised. TV and pressure are related by the equation:

Lung tissue compliance = change in volume / change in pressure

So, as a child's lung compliance worsens (decreases), the TV delivered will decrease for a given PIP. Similarly, if volume ventilation is chosen, the peak pressure will change based upon changes in lung compliance.

There are other characteristics of ventilators, such as the "mode", which should also be considered. These include:

Assist control modes: The ventilator delivers a set TV or PIP at a preset interval and with each patient's spontaneous respiratory effort (i.e., the patient's initial breathing effort, will trigger the ventilator to deliver another breath in synchrony). This mode is not commonly used in pediatrics.

IMV (intermittent mandatory ventilation): The ventilator delivers mandatory positive pressure breaths at a set rate. The patient may have unassisted spontaneous breaths between ventilator breaths, but the ventilator breaths are not synchronized with the patient's breaths.

SIMV (synchronized intermittent mandatory ventilation) pressure support: This method synchronizes the ventilator breaths with the patient's inspiratory efforts, thereby preventing the stacking of a ventilator breath on top of a spontaneous breath. Pressure support is the provision of a specified amount of positive pressure to assist the patient's own respiratory effort.

With some understanding of the modes of ventilation, the variables to be set on mechanical ventilators will be reviewed. These generally include respiratory rate (breath per minute), FiO2 (fraction of inspired oxygen), inspiratory time, and TV or PIP (depending on mode chosen). The starting respiratory rate (RR) is in part age determined, commonly: 30-50 in neonates, 25-30 in infants, 20 in children, 10-15 in teenagers. The rate is also dependent on the disease process. For example, patients who have air trapping/hyperinflation disorders (such as asthma) need a longer expiratory phase and therefore, a slower rate. You may have noticed that the set rate on the ventilator is often lower than that of a spontaneously breathing child of the same age/size. This is because the ventilator gives larger than normal tidal volumes "sigh breaths"). Spontaneous breaths are usually about 6-7cc/kg, whereas set tidal volumes are 10-l5 cc/kg. Recall that minute ventilation = TV x RR. So, if large tidal volumes are given, the RR needed to maintain the same minute ventilation will be lower.

In choosing a TV or PIP, the most important tenant to remember is, in general, to use a volume or pressure that causes good visible chest rise and air entry on auscultation. For TV ventilation, the starting range is usually about 10-l5 cc/kg. For pressure ventilation the pressure needed to move the chest will depend on lung compliance. A good way to judge this is to hand ventilate the child using an anesthesia bag with a manometer, to determine what pressure is required to move the chest. A typical range for a PIP in a lung with good compliance might be 16 to 20 mmHg vs up to 30 or 40 in a poorly compliant lung (20 being used for a mildly stiff lung such as a neonate with RDS).

The inspiratory time (IT or I-time) is also age and rate dependent and will also need to be altered depending on the child's disease. A guideline is 0.4-0.7 seconds for infants and 0.5-1 seconds for children and adults. Longer I-times increase mean airway pressure (by prolonging the inspiratory cycle) and therefore usually improve oxygenation.

In nonventilated patients, the glottis opens and closes during spontaneous respirations. Partial closure of the glottis provides a physiologic "PEEP" of 3-4mmHg by preventing complete emptying of the airway (i.e., we normally exhale against some resistance to maintain positive pressure in the alveoli during exhalation). In patients with good oxygenation and little pulmonary disease, a PEEP of 3-4 is adequate. Higher PEEPs are necessary for the patient with pulmonary edema, pneumonia, or atelectasis. High PEEP may also be useful for the post operative heart patient with surgical bleeding. Be aware that increasing PEEP increases mean airway pressure. Patients with high mean airway pressures may require volume infusions to maintain venous return and cardiac output. Inotropic support may also be needed in patients requiring very high PEEP (>10).

FiO2 is generally 100% during intubation but should be rapidly reduced, if possible, once mechanical ventilation is initiated. Weaning FiO2 can be done by monitoring pulse oximetry or ABGs. Oxygen is thought to be non toxic if the FiO2 is maintained at 40% or less. Since patients who are intubated are at high risk for ET tube plugging or displacement and resulting hypoxemia, we rarely reduce the FiO2 below 30%. Exceptions to this rule include children less than 34 weeks gestation (who are at risk for retinopathy of prematurity), and those with left to right shunts where the pulmonary vasodilation due to hyperoxygenation may result in excessive pulmonary blood flow. In general, saturations 95-100% are acceptable, although for children with severe ARDS (adult respiratory distress syndrome), BPD (bronchopulmonary dysplasia), or cyanotic heart disease, lower sats are expected/accepted.

In managing a ventilator, the settings of the ventilator should be adjusted to optimize the ventilatory support required by the patient. Too much oxygen or mechanical force may result in lung injury. Insufficient oxygen or mechanical force will result in hypoxia and hypoventilation. Assume that a normal blood gas is: pH 7.40, pCO2 40, pO2 100, BE 0, oxygen saturation 99% (refer to the chapter on interpreting blood gasses). In ICU patients, a higher pCO2 is sometimes tolerated (pCO2 45) to minimize ventilator trauma to the lung, and a lower pO2 is tolerated to minimize oxygen toxicity (oxygen saturation 95%). In premature infants, who are usually maintained with higher hemoglobins, lower pO2 values may be tolerated to minimize the risk of retinopathy of prematurity.

Adjusting the FiO2 will only affect the pO2 and oxygen saturation. Increasing the ventilator rate, will increase the minute ventilation so this decreases the pCO2 (and hence increases the pH). These are the two most basic changes that occur in ventilator management. One could also increase the minute ventilation (which would decrease the pCO2) by increasing the tidal volume (on a volume ventilator) or the PIP (on a pressure ventilator). Also realize that any parameter change which increases the mean airway pressure (MAP) will also increase the pO2. One could increase the mean airway pressure by increasing the PEEP, the inspiratory time, or the PIP. Increasing the tidal volume (TV) on a volume ventilator, in essence, increases the PIP so this also increases the MAP. Refer to the table below which describes the most commonly expected changes in pCO2, pO2 and MAP which occur with increases in the ventilator parameters in the column on the left:

Increase in:	pCO2	pO2	MAP
FiO2	no change	increase	no change
Rate	decrease	usually no change	increase
PIP/TV	decrease	increase	increase
Inspiratory time	usually no change	increase	increase
PEEP	usually no change	increase	increase

For example, a patient with an ABG: pH 7.28, pCO2 50, pO2 70, BE -3. One could improve oxygenation by increasing the FiO2, PEEP, IT, or/and PIP/TV. One could decrease the pCO2 and improve the pH by increasing the rate or/and PIP/TV. The best adjustment would be based on assessment of chest wall movement, aeration, expansion on chest x ray, the patient's pulmonary problems, and the current ventilator settings. For example, if the FiO2 is already at 95%, then it would be better to increase the PIP or IT rather than increase the FiO2.

Consider another ABG which may be encountered when the patient is improving: pH 7.45, pCO2 35, pO2 130, BE +0. The pCO2 is too low indicating that the minute ventilation is too high. The minute ventilation could be reduced by decreasing the rate and/or the PIP/TV. The pO2 could be lowered by decreasing the FiO2, PEEP, IT, and/or PIP/TV.

The rate and methods of weaning are quite variable, depending on the child's condition. It is therefore difficult to make general rules regarding this process. Some generalizations may be made:

The more acute the process, the faster weaning may take place.

ETCO2 monitoring or TCM monitoring may facilitate weaning and reduce the need for blood gases.

The child's baseline CO2 and O2 should be considered as weaning takes place. A "well" child with BPD may not have a normal CO2 of 40.

The child's clinical status should be considered as the weaning process takes place. An acceptable PCO2 is not evidence of "tolerating weaning" if the child is clinically in distress.

Prerequisites to extubation include:

1) A good cough/gag (to allow the child to protect their airway).
2) NPO about 4 hours prior to extubation (in case the trial of extubation fails and reintubation is required).
3) Minimize sedation.
4) Adequate oxygenation on 40% FiO2 with CPAP (or PEEP) = 4.
5) The availability of someone who can reintubate the patient, if necessary.
6) Equipment available to reintubate the patient, if necessary.

High frequency ventilation and negative pressure ventilation are specialized modes, which do not follow many of the "rules" of conventional ventilation. This is beyond the scope of this chapter but this is described well in a review article by Krishnan (4). High frequency ventilation is usually reserved for patients with very non-compliant lungs or those with air leak. Negative pressure ventilation (the old "iron lung" was a type of negative pressure ventilator) is infrequently used and is generally only useful for patients with neuromuscular disorders requiring long term ventilation at night.

Questions

1. SIMV stands for:
   a. synchronized intermittent mandatory ventilation
   b. simplified intermittent mechanical ventilation
   c. synchronized interspersed mechanical ventilation

2. Name 2 prerequisites for extubation.

3. True/False: The ventilator FiO2 should never be reduced below 40%.

4. True/False: There are very specific, pediatric evidence based protocols that will guide you, step by step, on ventilation management.

5. Minute ventilation = respiratory rate x _____

6. Physiologic PEEP is (in mmHg):
    a. 3-4
    b. 1-2
    c. 5-6

7. A good indicator of adequate tidal volume is:
    a. good chest rise
    b. adequate breath sounds
    c. oxygen saturation = 100%
    d. a and b

8. As compliance worsens in a child receiving pressure controlled mechanical ventilation, the TV delivered to the patient will:
    a. increase
    b. decrease

9. If the patient has the ABG: pH 7.28, pCO2 50, pO2 120, BE -3, which of the following ventilator changes would NOT be a good idea:
    a. decrease the FiO2
    b. decrease the I-time
    c. decrease the PEEP
    d. decrease the rate

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Answers to questions

1. a
2. Coughing or gag intact. NPO. Minimized sedation. Adequate oxygenation on 40% FiO2 with CPAP less than or equal to 4. Availability of personnel to reintubate if necessary. Availability of equipment to reintubate if necessary.
3. False
4. False
5. tidal volume
6. a
7. d
8. b
9. d

Chapter XIV.6. Submersion Injuries
Francisco J. Garcia, MD

A 14 month old male infant presents to the emergency department via ambulance in full arrest. His mother left him playing in the living room. After 30 minutes, she was not able to find him inside the house. He was found at the bottom of the swimming pool. The screen door which leads to the pool was found to be open. Initially, he was cold, blue and limp. She started CPR after calling 911. The EMS team performs CPR and resuscitation en route to the hospital. The infant is intubated and epinephrine is administered via the tracheal tube. An intraosseous (IO) line is started and epinephrine is given IO as well. After 35 minutes of resuscitation efforts in the emergency department, the infant is pronounced dead.

Submersion injuries, which include drowning and near-drowning continue to be one of the leading causes of deaths in children, after motor vehicle accidents and cancer. In the United States, approximately 5000 children and adolescents die every year as a result of submersion injuries (1,2). Submersion injuries have a bimodal age distribution. The first peak is seen in infants and toddlers less than 4 years of age, who are susceptible to submersion in swimming pools, baths or household buckets (2). Lack of caregiver supervision, neglect, and suboptimal barriers are contributing factors. The second peak occurs in adolescents and is associated with risk-taking behaviors as well as alcohol and drug use. Coexisting trauma and suicide intent should always be considered in this older age group (3).

Drowning is defined as death within the first 24 hours of submersion, which includes death at the scene. Near-drowning is defined as submersion in which survival is greater than 24 hours, regardless of morbidity and mortality. The common pathophysiologic events in all drowning incidents are asphyxia and hypoxia. After a submersion incident, most victims will go through a period of struggle and breath-holding, or water will enter the oropharynx and larynx resulting in choking and laryngospasm (4,5). This will lead to hypoxia and loss of consciousness, followed by asphyxia and death. Loss of protective reflexes will occur in most victims, leading to water aspiration. This is known as "wet drowning." In 10% to 20% of victims, intense laryngospasm persists and no significant amount of water enters the lungs, even though the victim is unconscious (4,5). This is also known as "dry drowning." A great deal of controversy existed in the past regarding the pathophysiology of drowning and near-drowning. Sufficient research data has shown that there are no significant physiologic differences between salt water and freshwater submersions or wet and dry drowning. Salt water submersion victims will likely be hypernatremic and fresh water submersion victims will likely be hyponatremic, but this difference does not appear to be clinically important in most instances, and is largely due to swallowed water rather than aspirated water.

All organ systems are affected after a submersion injury as a result of asphyxia, hypoxia and acidosis. Respiratory failure, aspiration pneumonia, barotrauma, and adult respiratory distress syndrome (ARDS) are frequent complications. Arrhythmias as well as cardiogenic shock may also be seen. Renal dysfunction is a common finding (acute tubular necrosis). Liver and gastrointestinal dysfunction may also occur. However, it is the irreversible hypoxic-ischemic damage to the brain that accounts for most of the long term complications (2,6). Risk factors that have been identified as indicators of irreversible neurologic injury and mortality include (2,6):

1) Age less than 3 years.
2) Submersion longer than 5 minutes.
3) Resuscitation not attempted for 10 minutes after rescue.
4) Seizures, fixed/dilated pupils, decerebrate posture, flaccid extremities and/or coma.
5) Asystole on arrival to the emergency department.
6) Arterial blood pH <7.1.
7) Elevated blood sugar level.
8) Glasgow Coma Scale <5.
9) Apnea after cardiopulmonary resuscitation.

A classification of submersion victims based on neurologic function was developed by Conn and Baker (7,8). This classification has several advantages: 1) It estimates the magnitude of hypoxic insult. 2) It guides the selection of appropriate therapy. 3) It is highly predictive of outcome. The classification is as follows:

Category A: Awake, alert, fully conscious, minimal injury.

Category B: Blunted, obtunded to stuporous, normal central respiratory drive, purposeful responses to pain.

Category C: Comatose. Unarousable, abnormal central respiratory pattern, abnormal motor responses to painful stimuli, seizures may occur. Category C is further divided into subcategories based on worsening CNS function: C1) Decorticate, Cheyne-Stokes respirations. C2) Decerebrate, central hyperventilation. C3) Flaccid, apneustic or cluster breathing. Manifestations of multiorgan dysfunction failure appear in category C (7,8).

The management of the drowning victim starts in the field with bystander cardiopulmonary resuscitation (CPR) after activation of the Emergency Medical System (EMS). The goal is to improve oxygenation and ventilation as rapidly as possible to minimize cerebral hypoxic-ischemic damage. The neck should be immobilized if there is a suspicion of spinal cord injury (e.g., intoxicated adolescent). Patients should be kept warm and dry. Hypotension should be treated aggressively. All patients should be transported quickly to the emergency department for further evaluation and treatment. Initially, vital signs and core temperature are obtained, followed by respiratory, cardiovascular and neurologic evaluation. Traumatic injuries should be excluded. Initial laboratory tests include: arterial blood gas (ABG), chest radiograph, electrolytes and serum glucose. Optional tests to be considered include: CBC, renal function tests, liver function tests and urinalysis. Even the ABG is optional in many instances since oxygenation can be measured via pulse oximetry and metabolic acid-base status can be determined from the serum bicarbonate. Most patients with a significant submersion injury should be admitted to the hospital for observation; however category A patients, with no other significant injuries, may be discharged from the emergency department after a period of observation.

Although the survival rate has improved with advances in emergency care, prevention is the best strategy. Parental supervision of infants and children while in and around water is essential. Early swimming lessons have not been shown to reduce the incidence of drowning. The policy statement published in 2000 by the American Academy of Pediatrics entitled, "Swimming Programs for Infants and Toddlers" does not endorse swimming instructions for infants and children until after their fourth birthday (9). Moreover, children and adolescents prone to conditions such as syncope and seizures should always have a partner. So far, the only environmental preventive strategy that has decreased the number of submersion injuries in children is the installation of four-sided fencing that isolates the pool from

the house (i.e., the house itself should not open directly into the pool area). Finally, all parents should be trained in cardiopulmonary resuscitation (CPR), since rapid institution of effective oxygenation and ventilation after a submersion injury has been associated with improved outcomes.

Questions

1. All of the following are considered risk factors for drowning except:
    a. Head trauma
    b. Alcohol use
    c. Upper respiratory infection with wheezing
    d. Seizure disorder
    e. Illegal drug use

2. True/False: The American Academy of Pediatrics advocates swimming classes for all children over two years of age.

3. Which of the following factors is associated with a poor outcome in a drowning case?
    a. Low blood sugar level
    b. Submersion longer than 5 minutes
    c. Drug or alcohol use
    d. Return of spontaneous cardiac rhythm following CPR
    e. CPR for less than 3 minutes

4. Which of the following interventions will improve the outcome in a drowning victim?
    a. Early intubation
    b. Transfer to a trauma center
    c. Intravenous access
    d. Early bystander CPR
    e. Cervical spine precautions

5. All of the following are complications after a submersion injury except?
    a. Adult respiratory distress syndrome (ARDS)
    b. Arrhythmias
    c. Renal dysfunction
    d. Hypernatremia
    e. Aspiration pneumonia

Related x-rays

Morisada MM. Near Drowning. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1996, volume 5, case 15. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v5c15.html

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Answers to questions

1. c
2. False. The AAP recommends against swimming lessons below the age of 4 years.
3. b
4. d
5. d. Hypernatremia may occur in a salt water submersion victim, but it is not considered clinically important in most instances and it is not considered to be a "complication".

Chapter XIV.7. Pneumothorax and Other Air Leaks
Edward W. Fong, MD

A father brings his 8 year old daughter into your office because "she is not able to catch her breath". He reports that she has just recently recovered from a cold, but has continued to cough. She often coughs in fits with post-tussive emesis, will sometimes turn blue in the face, and makes a "gasping-like" noise when she tries to inhale after a coughing episode. Currently, she complains about a pain in her chest and shortness of breath. According to her father, the onset of these symptoms began "after one of those coughing fits this morning". There is an ill contact in the house (a grandfather who has been coughing for the last 3 months).

Exam: VS T 37.1, HR 94, RR 28, BP 115/77, Oxygen saturation 93-95% in RA, height is 50-75th %ile, and her weight and head circumference are both in the 10-25th %ile. She is sitting on the exam table, leaning forward, taking quick breaths with some nasal flaring. She has slightly asymmetrical chest movements (her right chest wall moves less than her left) and she has decreased breath sounds with hyper-resonance and decreased tactile fremitus on the right as well. Her PMI and trachea are normally positioned, her sensorium is normal, and she has regular and symmetrical radial and femoral pulses. Since you suspect a pneumothorax, your nurse places the patient on 2 liters/minute of oxygen via nasal cannula while you arrange for medical transport to the Emergency Department.

Upon arrival at the ED, the patient's vitals are relatively unchanged except that her oxygen saturation is 100% on the 2 liters/minute of oxygen. She is switched to a non-rebreather mask with a FiO2 of 100% and sent for a PA and lateral CXR. Upon confirmation by the radiologist, she is diagnosed with a right, simple, primary spontaneous pneumothorax. It is estimated to be about 12% in size. She is admitted to the hospital for observation and continued oxygen therapy. She remains clinically stable overnight and her follow-up morning CXR showed a small decrease in the size of the pneumothorax. She is then taken off of oxygen and has another CXR performed the following morning. Although this CXR does not show any further decrease in the size of the pneumothorax, it had not increased. She is discharged home with instructions to follow-up with you the next day.

Air leak syndromes encompass a wide-spectrum of diseases including pneumomediastinum, pneumothorax, pneumopericardium, pneumoperitoneum, subcutaneous and interstitial emphysema, and pulmonary pseudocyst. Due to the pathophysiology of air leak syndromes, more than one of these disease processes are often present concomitantly. The exact prevalence and incidence of the differing air leak syndromes is hard to determine. The best estimates exist for pneumothoraces. From a study of Minnesota residents between 1959 and 1978, it has been estimated by extrapolating the data, that about 9000 people in the United States develop a primary spontaneous pneumothorax annually (1). In a recent American College of Chest Physicians (ACCP) Delphi Consensus Statement, it is estimated that, in the United States, both primary and secondary spontaneous pneumothoraces affect more than 20,000 patients and accounts for nearly $1.3 million in health care expenditures annually (2). Pneumothoraces are also found in about 5% of hospitalized asthmatic children and about 10-25% of cystic fibrosis patients older than 10 years old (3).

Thoracic air leak syndromes result from a free communication with the atmosphere, either from a pleura defect or from alveolar rupture. They are rarely caused by infection with a gas-producing microorganism (4). The type of air leak syndrome that develops will depend on the location and the nature of the communication. Although air leaks can be caused spontaneously, the majority of them are secondary to some type of trauma (intentional, accidental, mechanical, and iatrogenic). A retrospective case review by Kizer et al. found that over a 5 year period, 95% of patients who developed a pneumothorax while engaged in an outdoor sport had blunt chest trauma as the etiology (5). The mechanism of alveolar air leaks begins with positive intra-alveolar inflation pressure causing an increase in the air volume of the alveolus with a simultaneous decrease in the blood volume of the adjacent alveolar blood vessels. The difference between the changes in these respective volumes causes an attenuation of the tissue that tethers the perivascular sheath to the alveolar wall. When the traction force exceeds the tissue's tensile strength, a rupture of the base of the alveoli occurs allowing gas to escape into the perivascular space. The escaping air may then dissect along perivascular planes into the mediastinum (pneumomediastinum), into the pericardium (pneumopericardium), into the pleural space (pneumothorax), into the peritoneal cavity (pneumoperitoneum), out of the thorax along subcutaneous tissue planes (subcutaneous emphysema), and/or be confined to the interstitium of the lung (interstitial emphysema) (4). Since pneumothoraces are the most common type of air leak syndrome, the rest of the discussion will concentrate on this entity.

A pneumothorax is defined as the abnormal presence of air in the pleural space (6). Pneumothoraces are categorized as spontaneous or traumatic and classified as simple, communicating, or tension (1,7). Spontaneous pneumothoraces should be further categorized as primary or secondary. A primary pneumothorax occurs in an otherwise healthy person without underlying disease (rupture of a subpleural emphysematous bleb), while a secondary pneumothorax occurs as a complication of an underlying lung disease (COPD, tuberculosis, asthma) (1). Traumatic pneumothoraces may be caused by penetrating or blunt trauma, mechanical ventilation, central line placement, or toxic inhalations. A simple pneumothorax occurs when there is an accumulation of air without any communication to the atmosphere and without causing a shift of the mediastinum or hemidiaphragm. A communicating pneumothorax ("sucking chest wound") occurs when there is an associated defect in the chest wall (7). This defect may cause paradoxical chest wall movement (collapse during inhalation and expansion during exhalation) along with the sonorous sound of air entering and exiting the wound. A tension pneumothorax occurs when the progressive accumulation of air causes a shift of the mediastinum to the opposite hemithorax causing a subsequent compression of the contralateral lung and great vessels (7). Communicating and tension pneumothoraces may result in the rapid onset of hypoxia, acidosis, and shock.

Although the cardinal manifestation of a pneumothorax is the sudden onset of chest pain, symptoms will vary depending on the extent of lung collapse, degree of intrapleural pressure, rapidity of onset, age, and respiratory reserve of the patient (4,6). Symptoms that may be present include: tachypnea, dyspnea, tachycardia, and cyanosis. The chest pain may range from a localized sternal pain to an overwhelming pleuritic pain difficult to localize (6). Ipsilateral shoulder pain is common. There is usually a decrease in breath sounds, tactile fremitus, and a decrease in thoracic excursion while there is an increase in resonance to percussion on the affected side. Hamman's sign may be present in any type of air leak syndrome, which sounds like a fine rub (similar to Velcro). Hamman's sign is often mistaken for a pericardial friction rub.

If a tension pneumothorax is present, displacement of the trachea and PMI toward the contralateral side may occur as well as rapid deterioration with hypotension and bradycardia. In young children, tracheal displacement is not very common even with tension pneumothoraces.

The diagnosis of a pneumothorax should be confirmed by radiographs. Two views, AP and lateral, should be obtained. These may be supplemented by a cross-table lateral or lateral decubitus views. Expiratory views may help to visualize a small pneumothorax.

Radiographs will help to differentiate a pneumothorax from emphysema, an emphysematous bleb, diaphragmatic hernia, compensatory overexpansion, large pulmonary cavities, contralateral atelectasis, or other cystic formations. A CT scan is not necessary unless it is a recurrent primary spontaneous pneumothorax or a secondary spontaneous pneumothorax.

The treatment of a pneumothorax is determined by its classification. A tension pneumothorax usually results in cardiopulmonary compromise (shock, bradycardia, hypoxia) requiring immediate needle decompression (thoracentesis), which can be accomplished by inserting a large bore (16 or 18 gauge) needle (smaller gauge needles are satisfactory for premies, newborns and infants) through the second or third interspace (near the apex of the lung) in the midclavicular line. Immediate decompression cannot wait for radiographic confirmation. In fact it is often said, that if you see a tension pneumothorax on a CXR, the patient may already be dead or you are NOT looking at a tension pneumothorax, but something that is mimicking one instead. Tube thoracostomy (commonly called a chest tube) may be required after the initial decompression if the pneumothorax reaccumulates. A communicating pneumothorax should have the defect covered immediately, which helps to convert the condition to a simple pneumothorax. An occlusive dressing using petroleum gauze may be applied, but this must be done with caution as it can cause the development of a tension pneumothorax. Once the patient is in a hospital setting, he/she should be intubated and tube thoracostomy performed until she can be taken for definitive surgical repair.

There are two instances when a tension pneumothorax tends to occur more commonly: 1) positive pressure ventilation (i.e., in the ICU on a ventilator), and 2) external penetrating trauma (knife or bullet wound to the chest). The mechanics of this involve a valve effect of the air leak. A positive pressure ventilator pushes air into the pleural space through the leak, while during exhalation, the leak valve closes and does not permit the pleural air to escape. A penetrating wound to the chest may produce a slit into the pleural space, which sucks air into the chest when the patient inhales, but this air is trapped in the pleural space because the slit closes when the patient exhales. While a tension pneumothorax can occur in other conditions, it is largely these two conditions in which you are most likely to encounter a tension pneumothorax.

Management of a simple pneumothorax depends on its size and etiology. According to the ACCP Consensus Statement for primary spontaneous pneumothoraces, clinically stable patients with a small pneumothorax (occupying <15% of the hemithorax) (1) should be observed in the emergency department for 3 to 6 hours and discharged home if: 1) a repeat CXR demonstrates no progression of the pneumothorax, 2) the patient does not live a far distance from emergency services, and 3) there is reliable follow up care (2). If the patient is to be admitted to the hospital, oxygen therapy may be initiated since 100% oxygen will hasten the absorption of the pneumothorax (possibly by eventually enriching the pneumothorax with oxygen which is more soluble in blood). Clinically stable patients with a large primary spontaneous pneumothorax should be admitted to the hospital and undergo tube thoracostomy (2). The chest tube should not have negative pressure applied immediately, but rather it should initially be put to water seal to allow the trapped air to exit slowly. This precaution is done to avoid rapid reexpansion of the lungs, which can result in pulmonary edema.

The ACCP Consensus Statement for clinically stable patients with a small, secondary spontaneous pneumothorax recommends that these patients should all be hospitalized. The decision between observation and tube thoracostomy depends on the extent of the patient's symptoms, course of the pneumothorax, and practitioner choice (2). Clinically stable patients with a large secondary spontaneous pneumothorax should be treated similarly to the clinically stable patients with a large primary spontaneous pneumothorax. Any clinically unstable patient with a pneumothorax of any size should be immediately stabilized, decompressed, and hospitalized (2).

Procedures to prevent the recurrence of a pneumothorax should be reserved for secondary spontaneous pneumothoraces, a second episode of a primary spontaneous pneumothorax, or the persistence of an air leak regardless of whether or not it is the first episode of a pneumothorax. The procedure to prevent recurrence often involves bullectomy and/or pleurodesis usually through video-assisted thoracoscopy. However, the practitioner of a patient who may require lung transplantation in the future should consider consulting with the potential transplant team before undertaking pleurodesis.

The recurrence of spontaneous pneumothorax is common (40-87%), especially if the initial episode was slow to resolve (>7 days) or if the underlying disorder is not corrected (4). Activities that involve rapid or profound changes in barometric pressure (scuba diving, flying in unpressurized aircraft, etc.) should be avoided.

Pneumomediastinum and subcutaneous emphysema in the neck region are usually benign conditions if the patient is only minimally symptomatic, but they may precede a pneumothorax in some instances. If associated with respiratory distress, the air leaks signify a higher risk. Pneumopericardium is associated with cardiac tamponade and a high risk of mortality even if decompression is attempted.

Questions

1. True/False: A primary spontaneous pneumothorax in a tall thin boy does not require further work-up other than for treatment of the pneumothorax.

2. In order to emergently decompress a tension pneumothorax, one should insert a large bore needle between:
   a. the second and third interspace in the midaxillary line
   b. the fourth and fifth interspace in the midclavicular line
   c. either a or b
   d. neither a or b

3. List the different categories and classifications of pneumothoraces.

4. Pick the two conditions which you would most likely to encounter a tension pneumothorax:
   a. NICU ventilator patient for RDS.
   b. Near drowning patient on blow-by oxygen.
   c. Hydrocarbon aspiration.
   d. Blunt chest trauma.
   e. Stab wound to the mid lateral torso.

5. True/False: A chest tube is always the standard of care for the treatment of a pneumothorax.

6. A "sucking chest wound" refers to what kind of air-leak syndrome?
   a. Interstitial emphysema
   b. Simple pneumothorax
   c. Tension pneumothorax
   d. Communicating pneumothorax
   e. Pneumomediastinum

Related x-rays

Pneumothorax case: Yamamoto LG. Acute Chest Pain in a Tall Slender Teenager. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1995, volume 3, case 13. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v3c13.html

Pneumomediastinum case: Butts RJ. Hamman's Sign. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1994, volume 1, case 7. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v1c07.html

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Answers to questions

1. False. A patient with this type of body habitus should have a work-up that includes looking for a connective tissue disorder such as Marfan’s syndrome.

2. d. It is the second or third interspace in the midclavicular line or the fourth or fifth interspace in the midaxillary line.

3. Categories: Spontaneous and traumatic. Subcategories: Primary and Secondary. Classifications: Simple, Communicating, and Tension.

4. a & e. Tension pneumothorax is most likely to occur on ventilator patients and hose with penetrating chest trauma. A stab wound to the lateral mid thorax is very likely to have entered the lower thorax.

5. False. Treatment depends on the classification of pneumothorax.

6. d.

Chapter XIV.8. Trauma

Alson S. Inaba, MD
Rodney B. Boychuk, MD

A 3 year old boy was hit by a car as he ran out into the street to chase his soccer ball. When the paramedics arrived at the scene he was unconscious and had sustained multiple abrasions to his face, chest, abdomen and extremities. His right thigh was noticeably deformed and swollen. Because he demonstrated very shallow respirations, he was immediately intubated with in-line cervical spine immobilization. Two large bore IV lines where placed and he was then rushed to the trauma center.

Exam: VS T 37.0, P160, RR ventilated via the tracheal tube at 20, BP 100/80, oxygen saturation 97%. He is still unresponsive and being ventilated via the tracheal tube. His pupils are briskly reactive to light. There is excellent chest wall rise and fall via ventilation through the tracheal tube. There are numerous abrasions over his face, chest, abdomen and lower extremities. The abdomen is distended with decreased bowel sounds. His pelvis is stable, but his right thigh is obviously swollen and tense. Distal perfusion to all four extremities seems adequate. The remainder of his physical examination is unremarkable.

A CT scan of his head reveals a small occipital lobe contusion but no cerebral edema or hemorrhage. The CT scan of his abdomen reveals a small splenic laceration and a mild contusion of the left kidney. Chest and extremity radiographs reveal a displaced midshaft right femur fracture and a small left pulmonary contusion. His cervical spine and pelvic radiographs are normal. After appropriate stabilization interventions, he is admitted to the pediatric intensive care unit. His intracranial, pulmonary and splenic injuries are managed with supportive care and his femur fracture is reduced with open reduction and internal fixation. He is eventually discharged from the hospital approximately three weeks later, neurologically intact, and he is back to playing soccer a year later.

Each year there are approximately 1.5 million injuries sustained by children (1). Although the majority of these children recover uneventfully, the overall mortality rate of pediatric trauma is estimated at 1.5% (1). Each year, 250,000-500,000 children are hospitalized with various trauma-related injuries. Of these children who are hospitalized, 50,000-100,000 are left with some degree of permanent disability (1).

Blunt trauma accounts for approximately 87% of all childhood injuries, with penetrating trauma accounting for only 10% (2). Motor vehicle-related accidents are responsible for 40% of blunt pediatric trauma and are the leading cause of trauma-related fatalities in children (1). Injuries due to falls are the second most common etiology of blunt trauma in children.

Although children are susceptible to the same mechanisms of injury as their adult counterparts, a child's physiologic and psychologic responses to trauma are very unique. Thus a thorough understanding of some of the unique anatomic and pathophysiologic differences of children will enhance the quality of care that is provided during the evaluation, stabilization and management of the pediatric trauma patient.

One of the first very obvious physiologic differences between children and adults is the variation of normal pediatric vital signs based on the age of the child. A thorough understanding of pediatric vital signs is imperative in being able to detect very subtle abnormalities in a child's heart rate and respiratory rate. For example a subtle tachycardia may be the only clue to the possibility of early hemorrhagic shock in a child who otherwise looks stable. A subtle tachypnea may be the earliest clue to possible intra-thoracic injuries in a child with a normal room air oxygen saturation. Thus, anyone involved in the emergency care of children must be aware of normal vital signs based on a child's age. A simplified method to easily and quickly recall pediatric vital signs is as follows (3):

	Heart rate	Respiratory rate
Newborn to 1 year old	140	40
1 to 4 years old	120	30
4 to 12 years old	100	20
>12 years old	80	15

A summary of some of the key anatomic differences in children are as follows (1):

a) Smaller body size.
b) Larger head-to-body ratio.
c) Greater body surface ratio.
d) Shorter trachea and relatively larger tongue size.
e) Glottic opening more anterior and superior.
f) Less protective muscle and body fat.
g) Abdominal organs more anterior.
h) Growth plates of long bones are more susceptible to injury.

Because of a child's smaller body size, traumatic forces can be distributed over a larger surface area, thus making multisystem trauma the rule rather than the exception with childhood injuries (1). Children often times sustain internal injuries with minimal to no evidence of trauma on the external surface of their bodies. The internal organs of a child are more susceptible to traumatic forces because of their decreased amount of protective muscle and surrounding subcutaneous tissue mass. The spleen is the most commonly injured organ associated with blunt abdominal trauma. The increased flexibility and resilience of the pediatric skeleton and surrounding soft tissues also permits traumatic forces to be transmitted deeper into the internal structures. Thus as a general rule, internal injury cannot be ruled-out in a child merely based on the absence of external signs of trauma.

The larger head-to-body ratio of infants and young children makes them more susceptible to head injuries during falls. The larger head size also affects the fulcrum forces along the neck, making upper cervical spine injuries more common in infants and younger children as opposed adults who more commonly sustain injuries to their lower cervical spine. The larger head size as well as the increased body surface area in children make them more susceptible to greater heat loss and hypothermia when they are exposed during the trauma resuscitation.

The unique anatomic differences of the pediatric airway are critical to keep in mind when assessing and managing airway, breathing and ventilation in children. The shorter tracheal length, larger tongue size and the more anterior/superior location of the glottic opening are

key points to remember when attempting intubation in children. Because the pediatric epiglottis is less cartilaginous, use of a straight laryngoscope blade may facilitate intubation rather than the curved blades.

Pediatric head trauma is associated with the highest degree of morbidity and mortality. Injuries to the chest and abdomen also account for a fair amount of disability and death. Hypoxia and hemorrhagic shock are the final common pathways involved in pediatric trauma-related fatalities. Thus very strict attention to the assessment of a child's airway, breathing and circulation (ABCs of resuscitation) will reduce the morbidity and mortality of pediatric trauma.

The assessment and management of trauma patients is divided into the primary survey and secondary survey. The "ABCDE" of the primary survey involves the assessment of the following components:

A=Airway (cervical spine immobilization).
B=Breathing.
C=Circulation (with hemorrhage control).
D=Disability (a brief neurologic examination assessing the level of consciousness and pupillary size/reactivity).
E=Exposure (total exposure of the patient to be able to assess the entire body for possible injuries).

The major components of the primary survey therefore involve the assessment, stabilization and management of all acute, life-threatening conditions such as airway compromise, respiratory distress and hemorrhagic shock. This portion of the ABCs of trauma resuscitation are basically the same as in other resuscitation scenarios with two major caveats. These two caveats involve the possibility of cervical spine injury and hemorrhagic shock. The proper sequence that should always be adhered to in any resuscitation can be remembered by the mnemonic "A-I-R" (1):

A=Assessment
I=Interventions
R=Reassessment after each intervention

During the assessment and management the airway of any trauma patient, one must always consider the possibility of a neck injury and maintain cervical spine immobilization. This is extremely important if you are considering endotracheal intubation, during which time the airway should never be opened using the head-tilt maneuver. The jaw-thrust maneuver to open the airway with in-line cervical spine immobilization is the safest method to intubate any child with a potential cervical spine injury.

When assessing breathing and ventilation, always consider traumatic etiologies that could potentially compromise the child's ventilation and breathing such as open chest wounds, pneumothorax, hemothorax, rib fractures, flail chest and pulmonary contusions. Some of these traumatic etiologies may require immediate interventions such as needle thoracentesis and/or placement of a chest tube during the primary survey. Gastric distention which is also very common in pediatric trauma patients, can also compromise ventilatory efforts secondary to upward displacement of the diaphragm. Thus an orogastric tube may be helpful to decompress the stomach and thereby facilitate ventilatory efforts.

The most common etiology of shock in the pediatric trauma patient is hemorrhagic shock, although concomitant cardiogenic (e.g., cardiac tamponade), obstructive (e.g., tension pneumothorax) and neurogenic (e.g., spinal shock) may also exist. The increased reserve of a child's cardiovascular system allows children to compensate and maintain normal blood pressures despite even moderate degrees of hemorrhagic shock. Children will maintain a normal systolic blood pressure for age until they have lost up to 30% of their circulating blood volume (4). The circulating blood volume of a child is 70-80 ml/kg as compared to the typical adult circulating blood volume of 60 ml/kg. A normal systolic blood pressure for a child can be calculated via the formula: (Age X 2) + 90 mmHg. The corresponding expected diastolic blood pressure should be 2/3 X (SBP). The initial compensatory mechanism that one should look for during the early stages of hemorrhagic shock is tachycardia. The other compensatory mechanism that occurs to maintain normal perfusion and blood pressure is an increase in the systemic vascular resistance, which is manifested clinically by mottled/cool extremities, weak/thready distal pulses, delayed capillary refill time and a narrowed pulse pressure. If the early clinical signs of hemorrhagic shock are not identified and corrected, the child may progress to a preterminal stage of decompensated shock, which is defined as hypotension for age. Hypotension (systolic) in any aged child is defined via the formula: (Age X 2) + 70 mmHg. Thus a 5 year old child who presents with an initial systolic blood pressure less than or equal to 80 mmHg is already in the phase of decompensated shock and clinical has loss at least 30% of his circulating blood volume. The minimum systolic blood pressures for age are:

a) Newborns to 1 month old: >60 mmHg
b) 1 month old-1 year old: >70 mmHg
c) > 1 years old: (Age X 2) + 70 mmHg

The keys to the treatment of hemorrhagic shock in the pediatric trauma patient includes recognition of the early signs of shock, controlling any external sites/sources of hemorrhage, rapid fluid resuscitation to restore the circulating blood volume, early consideration of blood replacement therapy and an early involvement of the surgical team. Rapid fluid boluses are administered as 20 ml/kg of warmed crystalloid solutions (i.e., normal saline or lactated Ringer's solution are the only two acceptable solutions to use during fluid resuscitation). It is imperative to reassess the child's perfusion parameters after each fluid bolus in order to determine if additional fluid boluses will be required. If more than 40-60 ml/kg of crystalloid solution is required to restore adequate perfusion, blood replacement must then be considered. Blood replacement can be administered as either 10 ml/kg of warmed packed red blood cells (either crossmatched, type-specific or O-negative PRBCs, depending on how much time is available) or as 20 ml/kg of whole blood (not routinely available nowadays). Children who require blood replacement therapy may need surgical interventions to control the ongoing hemorrhage. Injuries that have the potential for extensive hemorrhaging include intra-abdominal and intra-thoracic injuries, pelvic fractures and femur fractures. As a general rule, it is taught that intracranial bleeds in themselves do not result in hypovolemic/hemorrhagic shock. The one exception to this rule involves head trauma in infants. Because the suture lines of an infant's skull are not yet fused, the skull has the capability to expand and accommodate large volumes of blood during acute intracranial hemorrhage.

If there is any difficulty in establishing intravenous access for fluid resuscitation and/or the administration of blood products, intraosseous (IO) lines should always be considered. IO line placement can be inserted just as quickly or even faster than venous cutdowns or central line placement. Although the previous Pediatric Advanced Life Support guidelines only allowed for IO line placement in children under 6 years of age, the current guidelines now have no age limitation for the use of IO lines in children. Although the ideal site for IO line placement in children is the proximal, medial aspect of the tibia (2-3 cm below the tibial tuberosity), an alternative site is the distal anterior aspect of the femur (2-3 cm proximal to the superior edge of the patella). Another alternative site in older children and

adults is the distal tibia (2-3 cm proximal to the medial malleolus). The only clinical contraindications for placement of an IO line in a child's leg during trauma resuscitation would include: a) a suspected fracture of the underlying bone in which the IO line is placed, and/or b) a suspected traumatic disruption of the venous return proximal to the site of IO insertion.

The secondary survey begins with a reassessment of the life-threatening problems addressed during the primary survey and is then followed by a complete head-to-toe physical examination to assess and manage any non-life threatening injuries that were not identified during the primary survey. The assessment and management of specific head, neck, thoracic, abdominal, pelvic and extremity injuries is beyond the scope of this text. However a high clinical index of suspicion based on the mechanism of injury should always guide one's assessment and management. Although a more detailed assessment of child abuse is presented in another chapter of this textbook, the possibility of nonaccidental trauma (i.e., child abuse) should always be considered under certain circumstances (4): a) A discrepancy between the history that is presented by the caregivers and the actual physical examination findings. b) Injuries that are incompatible with a infant's neurodevelopmental capabilities. c) A delay in seeking medical advice/treatment for what appears to be a serious injury. d) Findings of multiple injuries at various chronological stages. e) Bites marks, cigarette burns or rope/cord marks. f) Burns with sharply demarcated margins. g) Genital or perianal trauma (including burns to these areas). h) Multiple subdural hematomas. i) Retinal hemorrhages. j) Rib fractures involving multiple ribs and/or at various chronological stages.

Successful resuscitation of the pediatric trauma victim involves more than just a systematic approach to the primary and secondary surveys. It also depends upon a thorough understanding of the unique anatomic and pathophysiologic differences in children. By keeping these unique differences in mind, trauma teams will be able to decrease the morbidity and mortality of pediatric trauma by providing more efficient and appropriate care for the injured child.

Questions

1. The first priority in the resuscitation phase of any pediatric trauma patient is:
    a. To immediately establish vascular access.
    b. To establish and maintain patency of the airway while maintaining cervical spine immobilization.
    c. To obtain immediate x-rays and laboratory studies in order to ascertain the patient's overall status.
    d. To alleviate any pain with intravenous analgesics in order to facilitate a more reliable physical examination.

2. The leading cause of death in children >1 year of age is:
    a. Sudden infant death syndrome.
    b. Lethal cardiac dysrhythmias.
    c. Meningitis.
    d. Trauma.
    e. Leukemia.

3. The most common etiology of shock in the pediatric trauma patient is:
    a. Neurogenic shock.
    b. Cardiogenic shock.
    c. Anaphylactic shock.
    d. Hypovolemic shock.
    e. Tension pneumothorax.

4. The main goal of the primary survey of trauma resuscitation includes:
    a. Obtaining STAT portable radiographs of the neck, chest and abdomen.
    b. Assessment and stabilization of the child's airway, breathing and circulation.
    c. Obtaining immediate vascular access with a central line.
    d. Performing immediate endotracheal intubation to prevent aspiration.
    e. A trauma surgeon must be present to perform the primary survey.

5. All of the following statements regarding pediatric trauma are true except:
    a. The majority of pediatric trauma-related fatalities are due to motor vehicle related accidents.
    b. The majority of trauma that occurs in children is due to blunt trauma rather than penetrating trauma.
    c. Cervical spine trauma is more common than abdominal trauma.
    d. Multisystem trauma is common in children who sustain motor vehicle related accidents.

6. The abdominal organ that is most commonly injured in children is the:
    a. Duodenum.
    b. Pancreas.
    c. Liver.
    d. Kidneys.
    e. Spleen.

7. What area of the body is associated with the greatest frequency of serious injuries in children?
    a. Head.
    b. Neck.
    c. Chest.
    d. Abdomen.

8. Which of the following scenarios would be most suspicious for possible child abuse?
   a. A 2 year old who presents with a tibial fracture after reportedly falling down a few steps.
   b. A 1 year old who presents with a forehead hematoma after reportedly falling out of a stroller.
   c. A 3 month old who presents with a nondisplaced femur fracture after reportedly rolling off the changing table.
   d. A 3 year old who presents with a spiral fracture of the tibia after reportedly getting his leg twisted while falling off a tricycle.

Related x-rays

Yamamoto LG. Multiple Trauma in a 2-Year Old. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 2002, volume 7, case 8. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v7c08.html

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Answers to questions

1.b, 2.d, 3.d, 4.b, 5.c, 6.e, 7.a, 8.c

Chapter XIV.9. Toxicology

Alson S. Inaba MD

Case 1: A 2 year old boy reportedly ate 12 grape flavored chewable acetaminophen tablets that he found in the bathroom two hours ago. He already has had two episodes of vomiting. His mother calls the pediatrician and asks for advice. She states that her son is now playful and "looks fine." If you were this child's pediatrician, what recommendations would you give to his mother? In this case, the majority of the details regarding the ingestion are known yielding some data upon which treatment and management decisions can be made.

Case 2: A 15 year old girl reportedly took a whole box of diphenhydramine (Benadryl) tablets after she got into an argument with her boyfriend. She is brought to the emergency department by her parents who claim that she is "not acting right." She is slightly sleepy in appearance but seems to answer questions appropriately. She denies taking any other medications, alcohol or illicit drugs. She does not remember exactly when she took the diphenhydramine tablets. Her vital signs reveal HR 160, RR 18, BP 160/90, RA O2 sat 99%. Her physical examination is unrevealing. If you were the emergency department physician caring for this girl, what would be your assessment and plan of action? This case involves an intentional overdose situation involving a teenager which is a more difficult scenario to assess because the history that is provided is often incomplete and/or inaccurate/unreliable. For example, did she really ingest an entire box of diphenhydramine tablets as was reported? Is there the possibility that she ingested other substances in addition to the diphenhydramine? When did the reported overdose occur and is her degree of tachycardia and hypertension consistent with the medication that was allegedly ingested? Is it possible that this adolescent female is pregnant and if so, are any of your therapeutic interventions contraindicated in a pregnant female?

Case 3: A 3 year old boy is brought to the emergency department by the paramedics in status epilepticus. The father found his son seizing and immediately called 911. The child has never had prior episodes of seizures but he has had two days of low grade fevers along with a slight cough. He is not on any medications and his father denies any possibility of head trauma preceding the seizure. He requires IV anticonvulsants to terminate the seizure activity. Although you are contemplating the possibilities of meningitis and febrile seizures in your differential diagnosis, should the possibility of a toxic ingestion/exposure also be considered in the differential diagnosis in this case? This case illustrates how one must consider the possibility of a toxic exposure in the differential diagnosis of a patient who presents to the emergency department with severe, life threatening signs and symptoms (e.g., status epilepticus, coma, respiratory distress, cardiovascular shock, altered mental status, etc.).

Each year approximately two million poisoning cases are reported to poison control centers through the United States. Based on the 2000 Annual Report of the American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System, there were 2.1 million human exposure cases reported throughout the country last year (1). Keep in mind that the actual number of poisoning cases that occur each year is considerably higher than this since all poisoning cases that occur are not actually reported to a poison control center. The majority (75%) of these poisoning cases that are reported to the poison control centers each year are safely and effectively managed at home with phone advice from the poison control center's poison information specialists. Therefore only 25% of the callers are actually referred to emergency departments for further assessment and treatment.

Roughly 50% of the reported poisoning cases involve children under six years of age. Within the group of children that are <6 years of age, the largest group is the 18 month to 3 year age group. Therefore healthcare providers who deal with the pediatric population must be extremely knowledgeable in the assessment and management of poisonings. The substances that were most frequently reported involving poisoning in children under six years of age in the 2000 annual report are listed as follows: Cosmetics & personal care products (13%), cleaning substances (11%), analgesics (7%), foreign bodies (7%), plants (7%), topicals (6%), cough & cold preparations (5%), insecticides & pesticides (4%), vitamins (4%) (1).

Poisonings can occur through a variety of different routes of exposure, but the most common route of exposure is via oral ingestions. Each year approximately 75% of all poisoning cases are due to ingestions. Other routes are dermal (8%), inhalation (6%), ocular (5%) and bites/stings (4%).

The majority of the human exposure cases each year involve accidental exposures as compared to intentional overdoses. In 2000, 86% of the reported two million human exposure cases involved unintentional/accidental exposures, while only 11% involved intentional exposures (with the majority of the intentional overdoses involving adults) (1). Up to 90% of the poisoning cases each year occur in the victim's own home, while only 1% occur at schools.

The majority of the poisoning related fatalities each year involve adults. However each year approximately 20-35 of the annual fatalities unfortunately involve children under six years of age. In 2000, the substances that were responsible for these pediatric fatalities were: methanol, crotalid snake bite, pine oil cleaner, carbon monoxide/smoke, hair oil/conditioner, kitty litter (aspiration), lead, kerosene, aluminum phosphide pesticide, paraquat pesticide, acetaminophen, methadone, morphine, amitriptyline, diphenhydramine, norfloxacin, and diphenoxylate/atropine (antidiarrheal) (1).

The three clinical cases listed at the beginning of this chapter illustrate the wide spectrum of how poisoning cases may present to healthcare providers. Because it would be virtually impossible to cover every possible type of poisoning scenario that you may encounter in your career, a systematic and logical overall approach to poisonings will be emphasized throughout this chapter. Since 75% of all toxic exposures involve ingestions, this chapter will primarily focus on the assessment and management of toxic ingestions. Decontamination from ocular or dermal exposures basically involves copious washing/irrigation of the eyes or skin to prevent further absorption of the toxin.

The key points in the general approach to the poisoned child that will be covered in this chapter include the following:

1. Initial stabilization priorities
2. History (the What, When and How much of poisonings)
3. Decoding of the vital signs and the toxicologic physical examination
4. Toxidromes
5. Gastrointestinal decontamination and enhanced drug elimination
6. Laboratory studies
7. Antidotes and ongoing care
8. Patient disposition from the emergency department
9. Helpful poison prevention tips

The initial management of any poisoning case must first address the assessment and stabilization of the standard "A-B-C's" of emergency medicine. Regardless of what substance may have been ingested, the physician must assure that the child's airway, breathing and circulation have been assessed and stabilized first, before addressing other issues such as gastrointestinal decontamination and laboratory evaluations. If the patient is unable to maintain and protect his or her own airway or has a diminished gag reflex, one may need to first consider endotracheal intubation prior to performing any type of gastrointestinal decontamination in order to protect the airway from aspiration. One must also be ready to address and stabilize any seizures that the patient may be experiencing due to the toxic exposure. If a child develops hypoglycemic seizures secondary to a toxic ingestion, the child will require IV dextrose in addition to the standard anticonvulsant medications in order to eradicate the seizures. A rapid method to remember exactly how much IV dextrose to administer in these types of situations is my "Hawaii Five-O" rule (2).

An IV bolus of 0.5 gm/kg of dextrose will raise the patient's serum glucose level by approximately 60-100 mg/dL. Various concentrations of IV dextrose solutions (i.e., D5W, D10W, D25W or D50W) may be used to correct symptomatic hypoglycemia. A quick and easy method that I have devised to calculate how many "cc/kg" of any dextrose solution to draw up in order to administer 0.5 gm/kg of dextrose can be remembered by the following:

[dextrose concentration] x [?? cc/kg] = "50"

D5% 10 cc/kg
D10% 5 cc/kg
D25% 2 cc/kg
D50% 1 cc/kg

Therefore for a child with a hypoglycemic seizure, 5 cc/kg of a D10W solution would provide enough IV dextrose (0.5 gm/kg) to raise the child's serum glucose level by 60-100 mg/dL.

The three key questions that must be addressed in all poisoning cases are:

1) WHAT substance(s) was ingested?
2) WHEN did the ingestion occur?
3) HOW MUCH was ingested?

The answers to these questions will provide valuable information about:

a) The severity of the ingestion.
b) The potential benefits/efficacy of gastrointestinal decontamination.
c) Whether or not therapeutic interventions will be potentially necessary.
d) Accurate interpretation of specific drug levels.
e) Disposition of the patient (i.e., can the patient be safely discharged from the emergency department and after what period of time, or does the patient need to be admitted for further observation and treatment?)

When determining what substance(s) was ingested, one must be very specific. For example, many of the over-the-counter (OTC) medications frequently have various preparations with many different active ingredients. The exact milligram amount of the suspected ingested medication or liquid/syrup should also be confirmed since many medications (both OTC as well as prescription medications) are available in multiple milligram dosages and concentrations. If at all possible have a family member bring the bottle, box or container of the suspected toxin to the emergency department so that you yourself can verify the specific product and active ingredients. Local poison

control centers have computerized data bases of over a million substances, which can be accessed via a specific product name or via the individual active ingredients. If the suspected ingestion involved a plant, have a family member bring in as much of the actual plant for identification.

If the time from the ingestion to the time of arrival to the emergency department is within 1-2 hours, gastric lavage may be beneficial. In general, gastric lavage is not very effective if performed more than two hours post-ingestion. Knowing the time of the ingestion is also necessary when attempting to interpret specific drug levels. For example, an acetaminophen level of 100 mcg/ml cannot be interpreted and plotted on the nomogram unless the time of ingestion as well as the time of the blood draw are known. The level of 100 mcg/ml may not be toxic if it was obtained two hours post-ingestion, whereas the very same level would be considered toxic if it was obtained 20 hours post-ingestion.

Often, the most difficult aspect of the toxicologic history for the parents to answer is regarding the exact amount of the toxin or drug that may have been ingested. When confronted with this dilemma, the physician should always assume the worst case scenario rather than minimizing the amount that may have been potentially ingested.

The physician must be a medical detective in some aspects when attempting to estimate how much the child may have ingested. For example, if a child presents to the emergency department after potentially ingesting some tablets, questions which could be asked include the following (3):

a) Was the medication just recently purchased, and if so was the bottle completely full prior to the child getting to the pills?

b) If the bottle was not brand new or recently purchased, then how many pills were in the bottle before the child got to it?

c) If the medication was a prescribed medication, how many pills were originally prescribed, when was the medication prescribed and how many pills were already taken prior to the child getting to the bottle?

d) How many pills did the parents find remaining in the bottle?

e) How many pills did the parents find around the area where they found the child playing with the opened medication bottle?

f) How many pills did the parents find in the child's mouth?

Once the total milligrams of the potential ingestion has been determined, then one must calculate how much was ingested in mg/kg to determine severity potential. If more than one child may have been involved in an ingestion scenario, perform your mg/kg calculations for each child (based on each child's individual weight) assuming that all of the potentially ingested medication may have been consumed only by one child.

Although the majority of the substances that are typically ingested by children are either nontoxic or mildly toxic, there are a few substances that can potentially be fatal even when ingested in very small amounts. Some of these highly toxic substances with the corresponding amounts which could potentially be lethal for a 10 kg child are: amanita phalloides (one mushroom), amphetamines, antimalarials (one chloroquine tablet), calcium channel blockers (one nifedipine tablet), camphor (one teaspoon), clonidine (one 0.1 mg tablet), cocaine, cyclic antidepressants (one 150 mg imipramine tablet), ethylene glycol (one teaspoon), methylsalicylates (one teaspoon), narcotic medications, phenothiazines, theophylline (one 500 mg tablet) (4).

Toxic ingestions in children typically present to an emergency department in one of two scenarios. The first is that of a child who presents with a witnessed or suspected ingestion. The second scenario is that of a child who presents with a constellation of signs and symptoms which may include the possibility of a toxic ingestion within the working differential diagnosis. For example if a previously healthy 2 year old child presents to the emergency department after experiencing a brief afebrile seizure, the possibility of a toxic ingestion must be included within the differential diagnosis in addition to head trauma and other various etiologies for the child's afebrile seizure.

Every element of a child's vital signs must be carefully analyzed in any potential poisoning case scenario, which may give the physician a clue as to what the ingested substance might have been in the case of the unknown ingestion. The following is my quick and easy to remember method of simplified pediatric vital signs (5).

	Heart rate	Respiratory rate
Newborn to 1 year old	140	40
1 year old to 4 years old	120	30
4 years old to 12 years old	100	20
> 12 years old	80	15

The key elements of a toxicologic physical examination include the following elements (3):

a) Eyes: pupillary size, symmetry and response to light presence of nystagmus (vertical or horizontal).

b) Oropharynx: moist or dry mucus membranes, presence/absence of the gag reflex, presence of any particular or distinctive odors.

c) Abdomen: presence/absence and quality of bowel sounds.

d) Skin: warm/dry, warm/sweaty or cool.

e) Neurologic: level of consciousness and mental status, presence of tremors, seizures or other movement disorders, presence/absence and quality of deep tendon reflexes.

Toxidromes refer to a specific constellation of signs and symptoms which one may expect to see with a specific class or type of toxic substance. Toxidromes are based on the patient's vital signs as well as on the physical examination findings. The five distinct toxidromes and the common toxins of each of the toxidromal classes are listed below (3):

1. Anticholinergics (e.g., atropine, antihistamines, cyclic antidepressants, etc.): Tachycardia, hypertension, tachypnea, mydriasis, agitation, hallucinations/delirium, seizures, hypoactive bowel sounds, warm/dry skin, dry mouth.

2. Sympathomimetics (e.g., cocaine, amphetamines, PCP, decongestants, beta-agonists, theophylline, etc.): Tachycardia, hypertension, tachypnea, mydriasis, agitation, hallucinations, delirium, seizures, hypoactive bowel sounds, warm/sweaty skin.

3. Cholinergics (e.g., organophosphate and carbamate insecticides): "D-U-M-B3-E-L-S": Defecation, Urinary incontinence, Miosis, Bradycardia/Bronchospasm/Bronchorrhea, Emesis, Lacrimation, Salivation.

4. Opioids (e.g., codeine, morphine, meperidine, heroin, etc.): Bradycardia, hypotension, bradypnea, hypothermia, hyporeflexia, pinpoint, pupils.

5. Sedative-hypnotics (e.g., ethanol, benzodiazepines, barbiturates, etc.): Bradycardia, hypotension, bradypnea, hypothermia, hyporeflexia, miosis.

In 1985 ipecac administration was recommended in 15% of the poisoning cases handled throughout the country by the American Association of Poison Control Centers. However the recommended use of ipecac in the home has continually declined over the past several years to only 0.8% of poisoning cases reported in the year 2000 (1). Because of this, the American Academy of Pediatrics Committee on Injury and Poison Prevention is currently recommending that syrup of ipecac no longer be used as a poison treatment intervention in the home setting. The AAP is also recommending that pediatricians and other health care professionals advise parents to safely dispose of the ipecac syrup that they may currently have within their homes (6).

Gastric lavage has several clinical advantages over ipecac induced emesis. Gastric lavage provides a quicker, more controlled and safer route of gastric emptying than ipecac. The typical method of performing gastric lavage is to perform lavage with saline until the retrieved gastric contents are clear, then activated charcoal with sorbitol is instilled down the lavage tube.

Gastric lavage by itself is only effective at removing toxins that are still within the stomach. Lavage is not capable of removing any toxins that have already passed into the small intestines. Thus, if more than 1-2 hours have already elapsed prior to the patient's arrival in the emergency department, gastric lavage would probably not be very effective at preventing toxin absorption since the majority of the ingested substance has already probably passed out of the stomach and into the small intestines. In order to perform effective lavage, the internal diameter of the tube must be large enough to accommodate the pill fragments that are in the child's stomach. Thus, because large orogastric lavage tubes cannot always be safely placed in children, the option of gastric lavage may not be feasible and/or effective in smaller children. However, when the ingested substance is a liquid preparation, then a smaller sized tube would be sufficient, although it must be performed much sooner in order to be effective since liquid preparations are more quickly absorbed than pills or tablets.

Activated charcoal is very effective at adsorbing many ingested toxins and thereby prevents systemic toxicity. The majority of activated charcoal preparations currently available have adsorptive surface areas of 1,000 square meters per gram of charcoal. Some of the newer "super" adsorptive activated charcoal preparations reportedly have up to 2,000 square meters of adsorptive surface area per gram of charcoal. Because activated charcoal is able to prevent systemic toxicity by effectively binding so many different ingested toxins, many poison control centers have been recently recommending the administration of activated charcoal alone (without first performing gastric lavage) for ingestion cases of mild to moderate severity.

Although activated charcoal has been sometimes referred to as the "universal antidote" because it adsorbs so many different toxins, there are nine scenarios in which activated charcoal may not be clinically effective. My mnemonic to remember these nine scenarios is "C-H-E-M-I Ca-L Cam-P" (Cyanide, Hydrocarbons, Ethanol (and other alcohols), Metals, Iron, CAustics, Lithium, CAMphor, Potassium) (7). Even though charcoal has a very low affinity for cyanide, it may still be effective in preventing systemic cyanide toxicity if the amount of cyanide ingested is within the 100-500 mg range. Although charcoal is not necessary for ingestions of plain hydrocarbons, it should be considered if the ingested hydrocarbon contains systemic toxins (i.e., aromatic and halogenated hydrocarbons). If the ingested hydrocarbon does not pose any risk in terms of systemic toxic effects, charcoal administration should be avoided because the charcoal may predispose the patient to vomiting, which will definitely worsen the aspiration toxicity of the hydrocarbon. Although charcoal is very effective at adsorbing camphor, the administered charcoal may not be very effective depending on the time that the child presents to the emergency department. Because the majority of camphor containing products are typically found in liquid preparations, by the time the child presents to the emergency department, most of the liquid camphor has already been completely absorbed from the stomach and therefore there will be nothing left for the activated charcoal to adsorb. However if the child presents to the emergency department with 30 minutes after ingesting a potentially toxic amount of camphor, gastric lavage should probably be attempted in order to prevent systemic toxicity (e.g., camphor induced seizures). Multiple doses of activated charcoal (without cathartics) are sometimes used as a method of "gastrointestinal dialysis" for certain drugs that undergo enterohepatic circulation (e.g., theophylline, carbamazepine, cyclic antidepressants, phenobarbital, digoxin).

In the year 2000, activated charcoal was administered in 6.7% of the poisonings reported throughout the country (1). Although there have been a few studies that have looked at the efficacy of home administration of activated charcoal, the AAP does not currently recommend the routine use of activated charcoal as a poison treatment intervention in the home scenario at this time until their have been more studies which further investigate the risks and benefits of activated charcoal administration within the home (6).

Cathartic agents by themselves are not a very effective method of gastrointestinal decontamination. The main role of cathartics is to more quickly eliminate the charcoal bound toxin complex from the intestines before the toxins have the opportunity to dissociate from the activated charcoal. Sorbitol is the most commonly used of the cathartics because of its rapid gastrointestinal transit time. Sorbitol also comes premixed with activated charcoal ranging from 27-48 grams of sorbitol per 120 milliliter bottle of activated charcoal. Sorbitol can be safely used in children as long as it is administered only once per 24 hours and the stool output and the cardiovascular and hydration status are closely monitored.

Whole bowel irrigation (WBI) is a method of gastrointestinal decontamination that utilizes high volumes of iso-osmotic fluids to basically flush pills and other toxins out of the gastrointestinal tract. One advantage of WBI is that unlike gastric lavage, this method of decontamination will eliminate pills and toxins from the entire gastrointestinal tract and not just from the stomach. The second advantage WBI is that it can be utilized in those scenarios in which activated charcoal would not be very effective. The most common indication for WBI is an overdose of iron tablets.

The two iso-osmotic solutions which are currently utilized for WBI are GoLytely and CoLytely. Adults and teenagers can be given 1-2 liters of GoLytely per hour via a nasogastric tube until the ingested toxin is completely eliminated per rectum and the rectal effluent is clear in color. Typically the duration of WBI that is required to achieve this end point is roughly 4-6 hours. The recommended rate of WBI in children is 25 ml/kg/hour (up to a maximum 500 ml/hour). Any child undergoing WBI must also be carefully monitored for the risk of aspiration since high volumes of fluid may be required during this process.

Although there are multiple methods available to enhance the elimination of specific toxins from the body, the majority of pediatric poisoning cases can be treated with one or more of the decontamination methods mentioned above. The urinary pH can be manipulated in order to enhance the urinary excretion of certain drugs and toxins. The prime example is urinary alkalinization via the IV administration of sodium bicarbonate in order to enhance the urinary excretion of salicylates. Other more complex methods of enhanced elimination techniques include peritoneal dialysis, hemodialysis and hemoperfusion.

The exact laboratory tests which one would obtain in a poisoning case will depend upon the specifics of each individual case as well as the overall severity of the case. Although blood and urine toxicologic screens and specific drug levels may be obtained, the results of these studies typically are not available for several hours. Therefore, the initial stabilization and management of every poisoning case is clinically determined by the patient's presenting signs, symptoms, and vital signs. For intentional overdose cases, I would recommend an EKG rhythm strip (to quickly assess for any conduction abnormalities and/or dysrhythmias), acetaminophen levels, salicylate levels and a pregnancy test in females of child bearing age. An electrolyte panel may also be helpful to assess for metabolic acidosis. Once the results

of the electrolyte panel are known, one can also calculate the anion gap, which may provide helpful clues to the potential toxin in cases of the unknown or suspected ingestion. The anion gap can be calculated via the formula: Na - [Cl + CO2]

The calculated anion gap should normally be equal to 8-12 mEq/liter. Toxins that typically produce an increased anion gap metabolic acidosis may be remembered by the "M-U-D-P-I-L-E-S" mnemonic (Methanol, Uremia, DKA, Paraldehyde, Iron/Ibuprofen/INH, Lactic acidosis (e.g., carbon monoxide, cyanide and various other etiologies of lactic acidosis), Ethanol/Ethylene glycol, Salicylates).

Another very useful laboratory study is the measured serum osmolality and the serum osmolar gap. A patient's serum osmolality can be calculated via the formula:

2 x [Na] +[BUN/2.8] + [glucose/18]

Based on this calculated formula, the only three elements in the serum which are accounted for are the sodium, BUN and glucose. In contrast to this calculated formula, the actual measured serum osmolality also takes into account other substances in the patient's blood which could also affect the serum osmolality. Substances that classically elevate the measured serum osmolality (which are not part of the calculated osmolality) include the alcohols (i.e., ethanol, methanol, ethylene glycol and isopropyl alcohol). Thus a patient who has ingested one of the alcohols will typically exhibit an elevated measured serum osmolality despite a normal calculated serum osmolality.

The serum osmolar gap (measured serum osmolarity minus the calculated serum osmolarity) should be <5-10 mosm/Liter. The calculated osmolar gap is also valuable in that it can also be used to predict a patient's blood ethanol level via the formula:

[serum osmolar gap] x [4.6] = blood ethanol level in units of mg/dL

The 4.6 is a constant based on the density of ethanol. This factor will differ if the alcohol involved is something else such as ethylene glycol or methanol.

The mainstay to the treatment of the majority of poisoning cases involves supportive care and continued reassessment of the patient's airway, breathing and circulatory status. Although the majority of poisoning cases do not require any specific antidotes, some of the common toxins with antidotes are: acetaminophen (N-acetylcysteine), benzodiazepines (flumazenil), calcium channel blockers (calcium chloride), carbon monoxide (oxygen), cholinergics (atropine +/- pralidoxime), cyanide (cyanide antidote kit), cyclic antidepressants (sodium bicarbonate), digoxin (digoxin immune Fab antibodies), ethylene glycol or methanol (fomepizole), iron (deferoxamine), methemoglobinemia (methylene blue), opiates (naloxone), phenothiazine induced dystonic reactions (diphenhydramine), salicylates (sodium bicarbonate).

Because the majority of pediatric nonintentional ingestions typically do not involve highly toxic substances and/or large amounts, the majority of children who present to the emergency department with an accidental overdose can be safely discharged after a thorough assessment and an adequate period of observation. Hospitalization should be considered for the following situations:

a) Severe signs and symptoms upon presentation to the emergency department.
b) Unstable or abnormal vital signs.
c) A potentially severe ingestion based on the identity or potential toxic dose of the ingested substance.
d) Intentional overdoses.

Since prevention is the best method of reducing accidental poisoning in children, physicians should routinely incorporate poison prevention guidelines/tips into their healthcare maintenance discussions with their parents. Some of these points are listed below:

a) Keep the phone number of your local poison control center near the telephone.
b) If you suspect a poisoning, call the poison control center immediately for advice rather than waiting for your child to develop signs and symptoms of toxicity.
c) If you suspect a poisoning, never induce vomiting. Call the poison control center immediately for advice.
d) Store all medications and household products out of reach and out of sight (and preferably locked up).
e) Never refer to medicines as "candy," since a child may then try to eat more of the "candy," when you are least expecting them to.
f) Child resistant caps should be closed properly and remember that these types of caps are only child resistant and not "child proof".
g) Avoid transferring/storing household cleaning products, pesticides and automotive fluids in unmarked bottles or containers which could be mistaken for a beverage and consumed by unsuspecting child.

Questions

1. The majority of accidental ingestions in the pediatric population occur in which age group?
   a. 6 months to 1 year of age.
   b. 18 months to 3 years of age.
   c. 4 years to 6 years of age.
   d. 8 years to 12 years of age.

2. The most common route of toxic exposures is via:
   a. Inhalation.
   b. Dermal contact.
   c. Bites and stings.
   d. Ingestion.
   e. Ocular contact.

3. A mother of a 2 year old boy calls you because she suspects that her son may have eaten a few of his grandmother's "heart pills." She claims that her son seems fine and that the possible ingestion may have occurred 30 minutes ago. What is the best action for you to take as the child's pediatrician?

a. Have the mother induce vomiting immediately by sticking her finger in the child's mouth.
b. Immediately give the child eight ounces of water or milk to dilute the concentration of pills in his stomach.
c. Have her administer ipecac syrup immediately in order to induce vomiting.
d. Advise no interventions at the present time, but also advise her that if the child should begin to develop any symptoms to go to the emergency department for further treatment.
e. Call you local poison control center immediately for advice.

4. The gastrointestinal decontamination method of choice for a child who presents to the emergency department with multiple episodes of vomiting two hours after ingesting a toxic amount of iron is:

a. Syrup of ipecac.
b. Orogastric lavage.
c. Activated charcoal with sorbitol.
d. Multiple doses of activated charcoal.
e. Whole bowel irrigation.

5. A child with a suspected ingestion presents to the emergency department with delirium, tachycardia, mydriasis, dry mucus membranes and warm/dry skin. This child exhibits signs and symptoms of which toxidrome?

a. Anticholinergic.
b. Sympathomimetic.
c. Cholinergic.
d. Opioid.
e. Sedative hypnotic.

6. A parent suspects that her 18 month old son may have accidentally ingested a few pellets of rat poison. The mother should:

a. Not panic and simply wait to see if her son develops any signs and symptoms of toxicity before calling her pediatrician.
b. Call 911 immediately since this may be a medical emergency.
c. Call her local poison control center immediately for advice, rather than waiting to see if her son will develop signs and symptoms of toxicity.
d. Induce vomiting by giving her son a teaspoon of ipecac syrup.
e. Rush her son to the nearest emergency department for immediate gastric lavage and activated charcoal.

7. Activated charcoal would NOT be an effective method of gastrointestinal decontamination for which one of the following ingestions?

a. Albuterol.
b. Ferrous sulfate.
c. Amoxicillin.
d. Carbamazepine.
e. Phenobarbital.

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Answers to questions

1.b, 2.d, 3.e, 4.e, 5.a, 6.c, 7.b

Chapter XIV.10. Acetaminophen Overdose
Lynette L. Young, MD

A 16 year old female presents to the emergency department at 0500 with vomiting and nausea. Her mother reports that she (the patient) had an argument with her boyfriend last night. She woke her mom up early this morning saying that she feels sick. She admits that last night she took some pills at 2100. She has vomited 3-4 times at home. Her mom brought in the bottle of pills. She took acetaminophen 500mg tablets. Her mother reports it was a new unopened bottle with a quantity of 30 tablets. There are 8 tablets remaining in the bottle (maximum 11 grams of acetaminophen ingested).

Exam: VS T 37.2, P 88, R 18, BP 110/70, weight 50kg. She is alert, quiet, shaking her head yes/no to questions, with poor eye contact. Her skin is pink with good perfusion. Her oral mucosa is moist. Heart is regular with a normal rhythm and rate. Lungs are clear with good aeration. Her abdomen is soft, with normoactive bowel sounds, minimal epigastric tenderness, no rebound, and no guarding. She is alert, oriented, and walks about the room without difficulty.

She is given 50 grams of activated charcoal with sorbitol PO. She is also given 10 grams of N-acetylcysteine orally. An acetaminophen level, aspirin level, blood and urine toxicology screen and beta-HCG are drawn. The acetaminophen level drawn at 8.5 hours post-ingestion is 150 mcg/mL. She is hospitalized for further treatment as well as a psychiatric evaluation.

Acetaminophen (N-acetyl-p-aminophenol) or APAP is a common antipyretic and analgesic medication. It is a frequent toxic ingestion in young children and adolescents. Because acetaminophen is an ingredient found in many over-the-counter cold medications, it should be considered in intentional overdoses, as the patient may not realize that it is one of the components in the combination product taken.

Acetaminophen is metabolized in the liver via glucuronidation, sulfation, and through the cytochrome P-450 pathway. The majority of acetaminophen is metabolized via the sulfation and glucuronidation pathways into nontoxic products which are then excreted via the urine. Only a small percentage (5-15%) of the acetaminophen undergoes metabolism via the P-450 cytochrome oxidase system in the liver to produce the toxic intermediate N-acetyl-p-benzoquinoneimine (NAPQI). NAPQI is potentially toxic and may cause hepatic injury. However, the hepatic glutathione conjugates the NAPQI to produce APAP-mercapturate and APAP-cysteine which are both nontoxic metabolites. In severe overdoses, the glutathione stores become depleted and the toxic metabolite NAPQI builds up causing hepatocellular necrosis. In children 1 to 5 years, severe liver toxicity is rare with a single ingestion of acetaminophen, for reasons which are unclear.

There are four stages of acetaminophen overdose. In stage I (first 24 hours), the patient may have symptoms of anorexia, nausea, and vomiting. Sometimes they may have pallor and diaphoresis. In stage II (24-48 hours), the patient may show improvement in their clinical symptoms. The liver enzymes may begin to elevate. Stage III (72-96 hours) is called the hepatic stage. The patient may have vomiting, jaundice, abdominal pain, bleeding, confusion, lethargy, or even be in a coma. The patient may have coagulation defects, such as disseminated intravascular coagulopathy. The patient may progress to death. If the patient survives, the next period is stage IV (4 days to 2 weeks post-ingestion) which is called the recovery phase. Liver function tests return to normal in 1-3 weeks. Symptoms may resolve in 3-5 days.

In the management of acetaminophen ingestions the, basic principals of toxicology are followed. If it was an intentional ingestion, acetaminophen and aspirin levels should be obtained. Patients may present stating that they took "aspirin" when in fact they took acetaminophen. Blood and urine toxicologic screens should be done as well as a pregnancy test if the patient is a menstruating female. If the patient presents with altered level of consciousness, a co-ingestion must be suspected because acetaminophen does not produce any changes in mental status.

Acetaminophen is rapidly absorbed from the gastrointestinal tract. The peak plasma level ranges from 30 minutes up to 4 hours. Syrup of ipecac is not used as a form of gastrointestinal decontamination in the emergency department setting. Gastric lavage in a patient who presents to the emergency department is controversial. There are some toxicologists who feel that gastric lavage has not been proven to be helpful and should be used only if the ingestion is potentially rapidly fatal and the patient presents to the emergency department within 1 hour of the ingestion. In our patient's case, she was already vomiting so gastric lavage was not performed.

Another controversial area in the management of acetaminophen ingestion is activated charcoal administration. With intentional overdoses, there may be other occult co-ingestants that may be inactivated by the charcoal. Those that argue against giving charcoal believe that it may decrease the bioavailability of the antidote N-acetylcysteine (NAC). The proponents of giving activated charcoal recommend increasing the initial loading dose of NAC (140 mg/kg) by 30-40%.

For single acetaminophen ingestions a Rumack-Matthew nomogram is used to estimate the severity of the poisoning. The serum acetaminophen concentration is plotted against the time (hours) post-ingestion. The "toxic" level is a function of time after ingestion. If the APAP level is above the toxic level for that time after ingestion (i.e., the level is above the toxic line), there is possible risk for hepatotoxicity and NAC treatment is warranted. An acute single ingestion of acetaminophen of less than 140 mg/kg in children is likely to be nontoxic. There are some who have recommend a higher cutoff for the risk of toxicity in children, but there is no universal consensus on this. An adolescent/adult ingestion of 7.5 grams may be toxic to the liver. The acetaminophen level is best obtained 4 hours post-ingestion. The Rumack-Matthew nomogram is then used to interpret the level obtained. There are some that believe an acetaminophen level may be drawn as early as 2 hours post-ingestion in a child. They proposed that if the level is at or above 225 mg/L at 2 hours than treatment should be started (1,2).

The antidote NAC is available in the United States as an oral form which has an unpleasant odor and taste. An intravenous form is available in Canada and Europe but is not yet FDA approved in the USA. The patient may experience nausea and vomiting with the NAC treatment. Some suggestions include mixing it with soda or juice or administration via a naso-gastric or naso-duodenal tube. Antiemetics such as metoclopramide (Reglan) or ondansetron (Zofran) have been suggested. NAC given orally is very effective in preventing hepatotoxicity if it is given within 8 hours of the ingestion. If the ingestion has occurred close to this 8 hour time window, NAC should be given prior to receiving the acetaminophen level back from the laboratory, since waiting for the level will unnecessarily delay treatment. N-acetylcysteine is believed to act as a glutathione substitute. The sulfation is increased and less APAP is thought to enter the P-450 pathway so there is less toxic metabolite formed. Another theory is that NAC may bind directly to the toxic intermediates formed. The loading dose for NAC is 140 mg/kg. This should be increased by 30-40% if charcoal has been given. The dose is repeated if vomiting occurs within 1 hour. The maintenance dose is 70 mg/kg every 4 hours for 17 doses (total of 18 doses). There are some who advocate a shortened course of NAC treatment for those who are at low risk for hepatotoxicity (3,4). The alternative is to discontinue NAC if at 36 hours the liver transaminase level are normal and the APAP level is less than 10 mcg/mL.

The prognosis for patients of acetaminophen overdoses is generally good. Young children rarely progress to hepatotoxicity. Some believe that APAP is metabolized more via sulfation so there are less toxic intermediates formed. There are others that believe, since a child's liver and kidney are relatively larger than an adult, they are better able to clear the medication (5). Also children may vomit sooner after the ingestion, therefore eliminating the toxic substance. Children with accidental APAP overdoses are usually brought in earlier for medical care, as compared to adults with intentional APAP overdoses who typically present for medical care many hours or days after the overdose. Of the patients who progress past clinical stage III, 99% have clinical resolution.

Questions

1. The toxic intermediate N-acetyl-p-benzoquinoneimine is formed via which pathway?
    a. Sulfation
    b. Glucuronidation
    c. Cytochrome P-450
    d. Glutathionation

2. True/False: An adolescent presents with an acute ingestion of acetaminophen 5 hours prior. She is lethargic and is not responding appropriately. This clinical presentation is due to the acetaminophen toxicity.

3. If charcoal has been given, the dose of N-acetylcysteine should be increased by:
    a. Not increased.
    b. 5-10%
    c. 10- 20%
    d. 30-40%
    e. 50-60%

4. True/False: Hepatotoxicity is rare in children with a single dose acetaminophen ingestion.

5. N-acetylcysteine is most effective if given within how many hours of the acetaminophen ingestion?

6. Which is the first clinical stage that liver function tests may be abnormal?
    a. Stage I
    b. Stage II
    c. Stage III
    d. Stage IV

7. A patient arrives to the emergency department 7 hours after intentionally ingesting an unknown amount of acetaminophen. What should be done?
    a. Directly admit the patient to the floor and await a psychiatric consult.
    b. Draw a stat acetaminophen level and await the result before further treatment.
    c. Give the patient syrup of ipecac if she has not vomited and then administer activated charcoal.
    d. Draw a stat acetaminophen level and administer NAC.

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Answers to questions

1.c

2.False. Acute ingestion of acetaminophen does not cause altered mental status.

3.d 4.True, 5. 8 hours, 6.b, 7. d

Chapter XIV.11. Iron Overdose
Lynette L. Young, MD

A 2 year old boy presents to the emergency department with a chief complaint of blood-tinged vomiting. His mother was tending to her newborn infant when the patient climbed up and grabbed his mom's bottle of iron pills from the counter. He was able to open the bottle and thinking that the pills looked like candy, he ate them. His mother brought in her bottle of ferrous sulfate 325 mg (65 mg elemental iron) tablets. Counting the iron tablets in the bottle there is a maximum of 15 tablets missing (975 elemental Fe/12 kg = 81 mg/kg of elemental iron ingested).

Exam: VS T 36.9, P 120, R 30, BP 88/60, weight 12kg (10th percentile). He is alert, and being carried by mom. His skin is pink and warm with good perfusion and capillary refill. HEENT exam is negative. His oral mucosa is moist and there are no lesions. His neck is nontender. Heart regular rhythm and normal rate. Lungs are clear with good aeration. His abdomen is soft and slightly tender in the upper quadrants, with active bowel sound and no guarding. His distal pulses are strong and his distal extremities are warm. He is responding appropriately to mom.

An abdominal series reveals radiopaque tablets in the stomach and intestine.

Iron is a serious and potentially fatal ingestion. It used to be one of the leading causes of fatal poisonings in the pediatric age group. Toxicity is based on the amount of elemental iron ingested. The most common forms of iron include: ferrous sulfate (20% elemental iron), ferrous fumarate (33% elemental iron), and ferrous gluconate (12% elemental iron). Children's multivitamin with iron preparations contain 8 to 18 mg of elemental iron per chewable tablet. A common iron containing medication is a prenatal vitamin, which has 325 mg ferrous sulfate (65 mg elemental iron) per tablet.

Iron is absorbed in the intestine. The peak serum level ranges from 2 to 6 hours after ingestion of iron. Iron is absorbed in the ferrous (Fe++) form and is oxidized to the ferric from (Fe+++) within the cells. It is transported in the blood bound to transferrin. The iron binding capacity (transferrin level) is usually 300-500 mcg/dl (TIBC) and normal serum iron levels are 50-150 mcg/dl. There is usually no free iron circulating in the blood. The body has no specific way to excrete iron. Iron toxicity may result from the caustic/corrosive effect directly to the gastrointestinal mucosa. This may lead to perforation causing fluid loss from the gastrointestinal tract. Hypovolemia and shock may result. The second mechanism of toxicity is due to the presence of free iron in the circulation. Free iron may affect any organ including the kidneys, brain, lung, and heart. It builds up mainly in the liver. Free iron is found to concentrate in the mitochondria. Oxidative phosphorylation uncoupling is a mechanism for cellular toxicity. There are other unknown mechanisms for cellular injury. Lactic acidosis results from tissue hypoperfusion/cellular hypoxia. Free iron may also cause direct damage to the heart leading to decreased myocardial contractility (negative inotropic effect on the myocardium). Coagulopathies may occur from effects of iron on clotting factors.

There are four clinical phases of iron toxicity. In Phase I (0-6 hours), symptoms are due to the direct caustic/corrosive effect to the gastrointestinal mucosa. The patient may have symptoms of abdominal pain, vomiting (often with blood), and diarrhea. With severe iron poisoning, the patient may be lethargic or lapse into a coma. Shock and metabolic acidosis may result from blood and fluid loss and tissue hypoperfusion. Phase II (6-48 hours) is called the "honeymoon phase" or latent period. In this phase the gastrointestinal symptoms subside. There is an apparent improvement in symptoms. The patient may appear to be stabilized with appropriate therapy. Phase III (12 hours-5 days) is also known as the shock phase. There may be recurrence of gastrointestinal bleeding. Other symptoms in this clinical stage may include cyanosis, profound metabolic acidosis, coma, seizure, shock, and coagulopathy. The patient may have cardiac failure, renal failure, hepatic failure, and may go on to cardiovascular collapse and death. In Phase IV (2-6 weeks), the consequences of the corrosive effects of iron to the gastrointestinal mucosa may be evident. There may be scarring leading to strictures in the gastrointestinal tract. Obstruction may occur at the gastric outlet or small intestines.

A patient who has ingested less than 20 mg/kg of elemental iron and is asymptomatic can be observed. If the patient remains asymptomatic 4-8 hours after ingestion, he/she can be discharged to home. A serum iron level should be obtained on arrival to the emergency department if the patient is symptomatic or has ingested >60 mg/kg of elemental iron. A serum iron level should be drawn 4-6 hours post-ingestion if the patient is asymptomatic and has ingested 20-60 mg/kg or an unknown amount of elemental iron. With a serum iron level of less than 300 mcg/dl, the patient is usually asymptomatic. There is potentially moderate toxicity with an iron level between 300 to 500 mcg/dl. Serum iron levels greater than 500 mcg/dl fall in the severe toxicity range. If the iron tablet is enteric-coated or a sustained-released tablet, the absorption may be delayed and a second level drawn 6-8 hours after ingestion should be considered. The serum iron level may not be reliable if deferoxamine has been given. Other laboratory tests that are recommended are serum electrolytes, BUN, and creatinine. A baseline CBC can be drawn. An abdominal radiograph to look for radiopaque iron pills may be helpful. There are several tests previously used in iron poisoning which are no longer recommended. These include the total iron binding capacity (TIBC) (1) and the deferoxamine challenge test. They are not good predictors of toxicity. Also, previously recommended white blood cell count >15,000/mcL and blood sugar level of >150 mg/dL should not be used to predict the severity of iron overdose (2).

For patients with serious iron ingestion, treatment should include gastric decontamination, intensive supportive therapy, and deferoxamine administration. Gastric lavage should be done for patients with a large ingestion or if they are symptomatic. Whole bowel irrigation (WBI) is recommended if there are iron pills seen on X-ray and for any significant ingestion. The pediatric dose is 25-40 ml/kg/h up to a maximum of 500 ml/h. The dose in adolescents and adults is 1.5 to 2 L/h (3). This is continued for 4-6 hours or until the rectal effluent is clear. There are no studies to prove the effectiveness of whole-bowel irrigation in iron poisoning. A follow-up radiograph may be indicated. Activated charcoal does not bind iron well, but it can be considered if there is a co-ingestion.

Supportive treatment may include intravenous crystalloid fluids to treat shock. Dopamine and norepinephrine can be used if the hypotension persists. Blood component therapy may be needed for those patients with blood loss. Exchange transfusion is sometimes considered in young patients who worsen despite deferoxamine therapy although its effectiveness is questionable.

Deferoxamine chelates the ferric ion (Fe+++). It is given intravenously to patients who are symptomatic with vomiting, diarrhea, increased anion gap metabolic acidosis, gastrointestinal bleeding, lethargy, or hypotension. Deferoxamine therapy is also recommended if the serum iron level is greater than 500 mcg/dl. The iron-deferoxamine complex (ferrioxamine) is water-soluble and is excreted in the urine. It may cause the urine to be pinkish-orange ("vin-rose"). The initial dose of deferoxamine is 15 mg/kg/h. The rate may be increased up to 25 to 40 mg/kg/h. Rapid infusion of deferoxamine may cause hypotension.

Mortality is low in iron poisoning patients if they do not have shock or coma. With supportive treatment of patients with shock or coma, the mortality rate is about 50%. If deferoxamine treatment is added, the mortality rate drops to 10%. Patients may be discharged

home from the emergency department after 4-6 hours of observation if they are asymptomatic, have serum iron levels less than 300 to 500 mcg/dl, and have a negative abdominal X-ray. A psychiatric evaluation is needed if it was an intentional ingestion.

Questions

1. True or False: Charcoal is effective in binding iron and should be given in significant iron ingestions.

2. A 3 year old female (15 kg) ingested 15 of her mom's prenatal (325 mg ferrous sulfate) iron tablet. How much elemental iron per kilogram did she take?
   a. 15 mg/kg
   b. 25 mg/kg
   c. 45 mg/kg
   d. 65 mg/kg
   e. 85 mg/kg

3. Deferoxamine chelates the:
   a. Ferrous ion (Fe++).
   b. Ferric ion (Fe+++).

4. The two basic mechanisms of iron toxicity include:
   a. Direct corrosive effect on the gastrointestinal mucosa.
   b. Formation of a toxic metabolite.
   c. Binding to the protein transferrin.
   d. Toxic effect of the free ion.

5. Gastrointestinal symptoms may improve in which clinical (latent) stage of iron poisoning?
   a. Phase I
   b. Phase II
   c. Phase III
   d. Phase IV
   e. Phase V

6. True or False: Total iron binding capacity (TIBC) is a reliable predictor of toxicity in iron poisoning?

7. The whole bowel irrigation rate in children is?
   a. 5 ml/kg/h.
   b. 25 ml/kg/h.
   c. 75 ml/kg/h.
   d. 100 ml/kg/h.

8. The deferoxamine infusion rate should initially be started at:
   a. 15 mg/kg/h.
   b. 25 mg/kg/h.
   c. 40 mg/kg/h.
   d. 50 mg/kg/h.

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Answers to questions

1.False, 2.d, 3.b, 4. a & d, 5.b, 6.False, 7.b, 8.a

Chapter XIV.12. Child Abuse
Cynthia H. Tinsley, MD

A two month old male infant is brought to the emergency department (ED) with a chief complaint from the parents as having a "breath holding spell ". They describe the infant as turning blue and he stopped breathing. They shook the baby and blew a breath of air into his face. He started crying. There is no history of fever, coughing, congestion, vomiting or seizures.

He is the product of a full term delivery born to a 17 year old primigravida mother who is unmarried. She and the baby live with the grandmother. The 18 year old father is involved in the care of the baby. The infant's birth weight was 3.89 kg (8 pounds, 9 ounces) (90%ile). He now weighs 4.69 kg (10 pounds, 5 ounces) (25%ile). The mother says that the infant is doing well but he has not yet received any immunizations.

The infant is hospitalized for observation, monitoring and workup for an ALTE (apparent life threatening event) which could include the following: gastroesophageal reflux study, sleep study (for apnea), sepsis work up (CBC, blood culture, lumbar puncture, urine culture, chest x-ray). Since his growth percentile has fallen from the 90%ile to the 25%ile, a dietary history is obtained and the patient is observed in the hospital for weight gain. Since this is a single teenage mother, which places the infant at some risk for social and medical problems, a social work consultation is obtained.

The sepsis work up, reflux study and the sleep study are all normal. The dietitian determines that the mother, due to lack of knowledge, was giving the infant an inadequate amount of formula each day. He feeds well and gains weight in the hospital. The patient is sent home on a home monitor and the family is instructed to see the infant's primary physician in two days for follow-up weight checks.

He returns to the ED two months later (4 months of age) with repeated seizures during the afternoon. The mother describes that the infant fell off the couch at noon. He hit his face and had jerking motions of his arms and legs lasting 15 seconds. The mother states that the episode resolved and he seemed well. He was placed in a crib for a nap. Three hours later she went to his crib and found him having a tonic-clonic seizure of all extremities, which lasted one minute. He appeared lethargic. He vomited once and had three more similar episodes. When the grandmother returned home from work four hours later, they drove him to the ED where he is noted to be lethargic, with the following vital signs: P 120, R30, BP 70/40. Wt 6 kg (25%ile), Ht 66 cm (75%ile), HC 42 cm (50%ile). His exam is remarkable for a full fontanel, a weak cry, and dried blood on his upper gum with a frenulum tear. He has no signs of external head trauma or body bruises. His pupils are equal and reactive to light. The retina are difficult to examine.

When obtaining more history from the mother, she also notes that he still has not had any immunizations. She describes him as being irritable and a difficult baby to console, and a poor feeder. His stools are described as normal.

A CT scan of the brain shows a right subdural hematoma with generalized cerebral edema. He is admitted to the pediatric ICU. Initial labs are normal, but a skeletal survey demonstrates several rib fractures and a right tibia fracture. An ophthalmologist is consulted who determines that there are bilateral retinal hemorrhages.

What constitutes child abuse can differ among individuals and societies. In some societies child employment is viewed as abusive, while in others it is seen as necessary and normal. Child abuse must be defined within each society. We may define child abuse as any act that causes bodily injury, emotional or psychological harm, physical neglect or sexual abuse. Some child advocates strongly support a definition that includes not only overt acts that cause harm but includes acts that may have potential harm.

In the United States, federal and state legislation defines both child abuse and neglect. The Child Abuse Prevention and Treatment Act of 1974 (CAPTA) (1) is federal legislation that offers guidelines that states are required to incorporate into their legal definitions of child abuse. Each state develops its own definition based on these guidelines. Many states define abusive acts as ones that cause harm or potential harm. Some states specify conditions that are exceptions to the definition of abuse. An example of one such exception could be religious reasons for which parents choose not to seek medical care for their children. The parents would be exempt from charges of child neglect for not following medical advice. Other conditions that result from poverty, use of corporal punishment and traditional medical therapies may also be except in certain jurisdictions.

States are allowed to develop their own definitions of child abuse and neglect. Therefore they vary in how specific those definitions are. The definition may be very broad which allows the state child protective services to use their discretion in determining whether abuse has occurred. A common form adopted by states is a separate definition used for physical abuse, neglect, sexual abuse and exploitation, and emotional abuse. A few states have added abandonment in their definition of neglect.

In the state of Hawaii, child abuse has been defined as: the acts or omissions of any person that have resulted in the physical or psychological health or welfare of the child who is under the age of 18 to be harmed or to be subject to any responsible foreseeable, substantial risk of being harmed. The acts or omissions are indicated for the purposes of reports by circumstances that include but are not limited to (2):

1) When the child exhibits evidence of substantial or multiple skin bruising or any other internal bleeding, any injury to skin causing substantial bleeding, malnutrition, failure to thrive, burn or burns, poisoning, fracture of any bone, subdural hematoma, soft tissue swelling, extreme pain, extreme mental distress, gross degradation, death -- when such condition or death may not be the product of an accidental occurrence.

2) When the child has been the victim of sexual contact or conduct, including, but not limited to sexual assault as defined in the penal code, molestation, sexual fondling, incest or prostitution, obscene or pornographic photographing, filming, or depiction or other similar forms of sexual exploitation.

3) When psychological capacity of a child exists, as is evidenced by an observable and substantial impairment in the child's ability to function.

4) When the child is not provided in a timely manner with adequate food, clothing, shelter, psychological care, physical care, medical care or supervision.

5) When the child is provided with dangerous, harmful, or detrimental drugs.

All fifty states have specified which individuals are legally required to report potential child abuse cases. Generally people who have frequent interactions with children are mandated to report the case. Examples of professions that are frequently cited are teachers, social workers, law enforcement officers, health care providers, day care center employees, and coroners. Some states, such as Delaware, Florida and Tennessee require all individuals to be mandated reporters when they have a reasonable suspicion of child abuse.

How extensive is the problem of child abuse in the United States? In 1999 there were approximately 3 million cases referred to child protective services in the United States. In a third of these cases, child abuse was ruled out. Annually, there are 826,000 victims who suffer significant child abuse. Of these, approximately 480,000 (58%) were victims of neglect, 175,000 (21%) suffered physical maltreatment and 90,000 (11%) were subjected to sexual abuse (3).

The largest majority of children who are victims of child abuse are under the age of 3 years. This age group accounts for most of the fatalities. Of the 1100 children who died in 1999 of abuse, 470 (43%) of them were under 3 years of age and 946 (86%) of them were under 6 years of age. A significant number of these deaths are due to head injury, but neglect accounted for 420 of these deaths (3).

Child abuse can occur in any socioeconomic or cultural group. Epidemiological data has been reviewed to identify possible risk factors for the occurrence of child abuse. Factors that may have an increased risk include poor economic conditions (4), history of abuse in the caregiver, spouse abuse (5), premature infants, developmentally disabled children, and substance abuse in the caregiver. A history of a delay in seeking medical treatment, recent major stresses in the family, unrealistic expectations for the child, and a negative attitude toward the child are conditions that should alert the practitioner to the possibility of child abuse.

The types of physical abuse a clinician will encounter may range from bruising to severe head trauma with battering. A child may present with fractures, burns, cuts, bites, blunt trauma to the abdomen, and head trauma. To identify those injuries that are accidental and those that are intentional, a clinician must be familiar with the mechanisms of injuries, the developmental capabilities of the child and patterns of injuries.

DiScala et al, reviewed the differences between children who had injuries due to accidental trauma, and those who sustained injuries due to child abuse. In their review of over 18,000 children they found that children who were victims of child abuse were more likely to have been hurt by battering and shaking while accidental injuries were usually the result of falls. Abusive injuries were more likely to result in intracranial, thoracic and abdominal injuries. Child abuse resulted in more deaths, more severe injuries and more long-term disabilities (6).

One of the major keys in determining the difference between accidental injuries and abusive ones is that in abuse, the description of the incidents does not match the injury. A history of a minor fall in a child who presents with severe brain injury (brain swelling, subdural hematoma, ruptured intracranial blood vessels) is not compatible with a minor fall as the cause. The case at the beginning of this chapter presented a classic example of this, in which the history of a fall off the couch is alleged to have caused the seizures, cerebral hemorrhages, retinal hemorrhages and fracture.

Children may experience different fracture patterns than adults because of anatomical differences in the structure of their bones. The immature bone has different amounts of cartilage and the periosteum is thicker. Children have a growth plate and the metaphyseal and epiphyseal junction is prone to separation. Pediatric fractures are often associated with plastic deformation such that when the bone is bent, a permanent deformity occurs. The mechanism for fractures in children and adults can be the same, which includes blunt trauma to a bone with significant force to cause a fracture, twisting motions, and/or severe shaking that can fracture bones (7).

Injuries that are suspicious for child abuse are spiral fractures in non-ambulatory infants, which are due to twisting motions of the humerus and/or femur. The metaphyseal fractures of long bones that are often associated with severe shaking are particularly suggestive of child abuse. As occurred in the case study of this chapter, children who present with rib fractures without a history of significant chest trauma, are suspected of child abuse. Posterior rib fractures in a child who only has a history of minor falls are specific for intentional trauma. Other types of fractures that should alert the practitioner are multiple fractures, fractures of different ages, and a patient with fractures and other associated injuries. It is important to emphasize that a clinical history that is inconsistent with the type of fractures should raise suspicion of child abuse (8).

Skull fractures are the second most common skeletal injury seen in abused children (9). These fractures are often associated with intracranial injuries unlike unintentional injuries that are usually uncomplicated simple fractures. The size, location, numbers and whether a skull fracture is depressed is dependent on the degree and velocity of the force that impacts the child's head. It is important to emphasize that a clinical history that is inconsistent with the type of fracture should raise suspicion of child abuse. It is not credible that a child who is one month old can roll off a bed and fall a short distance to a carpeted floor and sustain a severe skull fracture with intracranial bleeding and retinal hemorrhages.

Bruising is due to bleeding into the dermis. Bleeding may be secondary to local trauma, coagulation abnormalities from clotting factor or platelet deficiencies, and vasculitis from various causes. Bruises have a tendency to follow different staging as they resolve. The area may initially be swollen, then turn a red or reddish blue color, then progress to green, yellow, brown, before clearing. Many authors have attempted to age bruises by their appearance. Many variables can affect the progression of a bruise including difference in circulation to the area, thickness of the skin, and depth and location of the bruise. Dating bruises to precise days or weeks, therefore, has been called into question (10).

Bruising is the most common external sign of child abuse, and it is also common in everyday childhood activities. As toddlers and children move forward, they may fall or bump into objects that can lead to bruising. Normally children who fall develop bruises that are located on their forehead, elbows, shins, and knees. Areas that are more likely to be bruised due to intentional injuries are the buttocks, genitals, perineal area, chest and back. Some bruises show patterns that may suggest the form of trauma. Examples are slap marks from fingers, bite marks, and pinching areas like the nose or ear lobes.

Some bruises are marks left by objects that are used to strike a child. Marks that look like loops are due to cords or rope that are looped before hitting a child. Bruising patterns have been described that match a belt buckle, spatula, iron, knife wounds, hairbrush, teeth marks, and numerous other objects. Often when authorities visit the home to investigate child abuse allegations, these objects are located.

Burns whether inflicted or accidental have a significant morbidity, mortality, and can require extensive medical, surgical, and physical therapy. These children may require plastic surgery and reconstructive surgery over months to years and sustain life long deformities. It is the obligation of health care providers to recognize those injuries that are suspect of child abuse and make reports to appropriate agencies.

A child may be burned from contact with hot liquids, hot objects or direct flames. Burns caused by hot liquids can have characteristic patterns when a toddler pulls a pot of hot liquid down or when someone pours a liquid over them. The liquid rolls down by gravity. The areas touched first receive the hottest liquid and the deepest burn, and those further down are less severely burned as the liquid cools. Since the liquid spills in a random splash, the burns are random. Immersion burns are more characteristic of child abuse. The child is held in hot liquid that creates burn lines where there are clear lines of demarcation of spared and burned areas. These burns may include the lower limbs only or the buttocks and perineum. Children who are put in hot water in a sitting position have a characteristic central clearing where the child's buttocks touches the bottom of the bathtub (which is slightly cooler). Limbs that are immersed have a demarcation that gives a stocking or glove pattern.

Cigarette burns are not uncommon skin lesions seen in child abuse. The marks left are circular with a deep center and devoid of hair. Toddlers may walk into a cigarette but these burns are not as deep and they are usually a single burn on the face or hands. Multiple cigarettes burns or burns located on the back, chest or legs are consistent with child abuse.

Lesions that can mimic child abuse include "coining" which is an Asian home remedy of heating coins and rubbing them on the child's back, which leaves linear bruising. Impetigo has been mistaken for cigarette burns. Bruising due to bleeding disorders like hemophilia, or platelet disorders, Henoch-Schonlein purpura, or Mongolian birthmarks have been misdiagnosed as inflicted injuries. Fractures may be due osteopenia in disabled children, and occult forms of osteogenesis imperfecta can be associated with pathologic fractures and bruising.

Children can be subject to numerous physical injuries but head trauma is the most common cause of death. The injuries can be due to direct impact or from acceleration and deceleration injuries. Patients can then develop extracerebral bleeding due to tearing of bridging vessels causing subdural and/or subarachnoid bleeding. The subdural hematomas often extend into the interhemispheric fissures. Cerebral edema often develops and may be the result of anoxia, poor perfusion, and/or direct tissue injury. While the areas of bleeding may be small on imaging studies, this does not reflect the degree of cerebral injury which is often substantial. Cellular death and axonal shearing are not easily visualized on CT scans. Neurosurgical evacuation of hemorrhage does not repair cerebral cellular and axonal injury.

These injuries are more common in infants and are the result of shaking battered child syndrome (also called shaken baby syndrome). Infants are more susceptible to these types of injuries due to the higher water content of the brain, poor neck control, proportionally larger head size, and more demyelinated nerve cells. The outcome of these injuries can result in brain death, cerebral atrophy, and chronic subdural collections. These children may remain in a coma, have developmental delays, seizure disorders, blindness and/or deafness (11).

The clinical presentation of shaken baby syndrome is often vague. There is usually minimal or no history of trauma and the spectrum of clinical signs range from poor feeding, vomiting, seizures to complete cardiopulmonary arrest. The symptoms are the result of intracranial injuries which may include subdural hemorrhage and/or subarachnoid hemorrhage, cerebral edema and shearing injuries to brain cells (12). Often these infants have no outward signs of abuse. Their intracranial injuries are associated with retinal hemorrhages and sometimes with long bone fractures or rib fractures. Since victims of shaken baby and other forms of child abuse can present with various signs and symptoms that at first glance may not suggest intentional trauma, the practitioner must have a high index of suspension and include child abuse in the differential diagnosis.

Besides head trauma, children may experience abdominal or thoracic injuries. These occur less often than other forms of physical injury. Abdominal injuries are most likely due to blunt trauma and can result in hematoma or laceration of the pancreas, duodenum and or the jejunum. These injuries can lead to hypotension, abdominal distention, vomiting, and ileus. These patients respond well to medical treatment. Blunt abdominal trauma may also result in visceral rupture to organs such as the liver, spleen pancreas, or major abdominal vessels. These children present very ill in shock with significant hemorrhaging, hypotension and possibly a full cardiopulmonary arrest.

Determining whether injuries sustained by infants and children are due to abuse or accident, can be difficult. The clinician should be alert to histories that do not adequately explain the injuries. It is then important to perform a complete assessment.

First and foremost, it is important to obtain a full medical history, which should include a complete description of the event in the caretakers own words. A story that is suspect, is one that does not match the injuries and changes over time. Include a developmental history and the current developmental capabilities of the child. Often, the history may include acts performed by the child that they are not developmentally capable of. For example, a seven month old infant is reported to have turned on the hot water faucet and got in the bath tub of hot water, when at seven months, they are not ambulatory, nor can they turn a faucet. Ask questions to determine if the family keeps medical appointments, the support system for the family, if any family stresses are present, the caretaker's perception of the child, and how they use discipline. Also obtain information about other hospitalizations, surgeries or previous injuries. A history of visiting multiple emergency rooms and numerous physicians may be a clue to attempts to avoid being reported to child protective services.

The physical exam should be complete and a record made of all outward signs of abuse. A body diagram should be used to describe the location, size, number, and characteristics of skin lesions. Good quality photographs should be taken to record the lesions. It is important to obtain measurements of height, weight, and head circumference and determine where the child plots on a growth curve. If there is any suspicion of sexual abuse, a specialist trained to do a complete medical and forensic evaluation should be consulted. Often a funduscopic exam is required to determine if retinal hemorrhages are present, and this exam is best done by an ophthalmologist after giving medication to dilate the pupils.

Laboratory tests and X-rays, will in part be determined by the clinical presentation of the child. Full skeletal survey x-rays should be obtained to diagnose obvious fractures and to look for occult fractures. A nucleotide bone scan may be considered because it may identify new fractures more clearly. The fractures should be aged as new or dated in various degrees of healing. Other x-rays to consider are chest x-ray, MRI or CT of the head and abdomen especially if there is any suspicion of possible intracranial or abdominal injuries. A CBC looking for any anemia or thrombocytopenia, electrolytes, PT, PTT, blood and urine cultures should be obtained. Other laboratory results to consider are liver enzymes and lipase if abdominal injuries are suspected.

Initially, a clinician, may not be able to confirm the presence of child abuse. However, the law requires that any suspicion of child abuse must be reported. Definite and/or severe cases of child abuse will require hospitalization or removal of the child from the home immediately. However, cases which are not confirmed and/or are not as serious, represent a dilemma for the clinician. Hospitalization and immediate foster placement is not necessarily indicated. But an immediate report to child protection authorities is still required because there is suspicion of child abuse. Should parents be told that you are about to report these circumstances to the child protection authorities? The answer to this is controversial, but it may be better to be honest with the parents, since they will probably find out who reported the incident later on. The best way to inform the parents that a report to child protection authorities is about to be made, is to point at an X-ray or injury and inform them that, "Whenever this type of injury occurs" (while pointing at the X-ray or injury), "the law requires that I report this to the child protection authorities. They might call you, so tell them what happened." If there is a fracture on an X-ray, point at the X-ray when saying this. If there is a bruise or burn, point at the bruise or burn when saying this. This is perceived as non-judgmental. It is almost as if you are reporting the X-ray or the injury, and not the parent or child. Compare this to "I have to report this to the child protection authorities, because this is suspicious for child abuse." This latter method often results in hostility, while the former method is non-judgmental which most often results in a neutral response from the parents.

There are unique forms of child abuse such as failure to thrive, Munchausen syndrome by proxy, maternal drug abuse and sudden infant death syndrome. Munchausen syndrome by proxy is a form of recognized child abuse in which a child presents with unexplained illnesses that are either fabricated or inflicted by the parents. Most often it is the mother who is the perpetrator. There are case reports of mothers that go to great lengths to make their children appear ill. Mothers have administered medication such as ipecac syrup to induce

vomiting, injected feces under the skin to produce infection, and induced apnea with a pillow over the child's head. Common characteristics of this syndrome include: 1) a child presenting with recurrent illnesses, 2) the parent has some medical knowledge, 3) the mother does not seem concerned about the child's illness, 4) the mother is hypervigilant in the hospital and will not leave the child's bedside, 5) the symptoms do not occur when the mother is away from the child, and 6) the father is often absent (13).

What is sudden infant death syndrome (SIDS) and how does it relate to child abuse? It is the sudden death of a child less than one year of age with no identified cause following a thorough investigation including an autopsy, and death scene investigation. Most cases are infants between 1 and 5 months of age. SIDS deaths occur more often in the winter months, and an association has been postulated with sleeping position, parental smoking or drug abuse, and infant and parent co-sleeping. Although most infant deaths are determined to be due to SIDS, a few deaths have proven to be infanticide. Further studies have identified infants initially presenting with recurrent apneic or cyanotic episodes, who were in fact victims of attempted suffocation (14).

Failure to thrive is defined as a child whose weight is below the 5th percentile for age. Organic causes of failure to thrive are numerous. A thorough history and physical examination will usually identify an organic cause due to neurologic, cardiac, gastrointestinal, genetic, endocrine or respiratory problems. A history of feeding practices, caloric intake and the child's ability to swallow needs to be evaluated. Laboratory studies may include a CBC, urinalysis with culture, blood urea nitrogen, creatinine, calcium, electrolytes, albumin, HIV testing and/or sweat chloride. If no organic cause can be determined, psychosocial causes need to be considered. Common causes are poverty, poor parental-child interactions, and child abuse. The child height, weight and head circumference should be plotted on to a growth chart. Children with non-organic causes of growth failure will show first a loss of weight, then height and lastly a decrease in head circumference. The practitioner may consider admission to the hospital to evaluate the parent-child interaction and the child's ability to gain weight with appropriate caloric intake. If the child gains weight quickly in the hospital with adequate calories, the diagnosis of nonorganic failure to thrive is highly probable. Once this diagnosis is made, a multidisciplinary approach to therapy to required to treat the psychosocial and economic causes while ensuring the safety of the child. Physicians, dietitians, social workers, nurses, and child protective services personnel may all be needed (15).

Perinatal drug abuse can have adverse effects on the fetus and newborn infant. Drugs used by the mother can have teratogenic effects on the fetus, cause premature delivery, growth retardation and cause withdrawal symptoms in the newborn. Perinatal substances abused include cocaine, amphetamines, alcohol, heroin, methadone, and barbiturates. Newborn withdrawal symptoms may include apnea, poor feeding, lethargy, seizures, irritability, tremors, and weight loss. Testing the newborn includes urine or meconium for drug exposure. The testing of newborns can bring into question confidentially concerns, and legal issues. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologist have taken the position that neonatal drug testing should be preferably performed with the consent of the mother. The information should be used to support rehabilitation of the mother and fostering healthy mother and child interactions without criminal prosecution. However, many states require referral to Child Protective Services and define perinatal drug abuse as child abuse and neglect. States such as California have committed to offering services such as education, and treatment for abuse.

Child abuse is a condition which medical practitioners who care for children will encounter in their practice. Our primary responsibility is the safety and welfare of the children in our care. To ensure that goal is accomplished, we must be advocates for the child and be vigilant in reporting any suspicious child abuse case.

Questions

1. A one year old child presents with facial bruising and a spiral fracture of the right femur. The parents state the child was bouncing on the bed and fell off and hit a nightstand. The leg is splinted in the emergency room. The patient has stable vital signs and does not appear to be in any pain. Child protective services has been contacted and a report has been filed. The hospital social worker wants to discharge the patient home pending the investigation. This child is medically stable for discharge. Should he be sent home?
2. What is Munchausen syndrome by proxy?
3. Define failure to thrive?
4. What is the key to determining nonaccidental injury as opposed to accidental injury?
5. True/False: Bruises that have different coloring can be used to date the time of the injuries.

Related x-rays

Shaken baby case: Yamamoto LG. Toxic Infant With a Full Fontanelle. In: Yamamoto LG, Inaba AS, DiMauro R (eds). Radiology Cases In Pediatric Emergency Medicine, 1994, volume 1, case 1. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v7c08.html

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Answers to questions

1. This child should be admitted to the hospital for his initial management and evaluation of potential child abuse. The hospital can offer the necessary diagnostic studies necessary to determine the presence and extent of other injuries. In addition the hospital environment offers and opportunity to observe child and family interactions by trained staff. It is the obligation of those caring for this child to insure that he be returned to a safe environment (16).

2. It is a unique from of child abuse where the child's caregiver inflicts or fabricates illness on the child.

3. When a child's weight is plotted on a growth curve and is found to be below the 5th percentile for their chronological age.

4. One of the major keys in determining the difference between accidental injuries and abusive ones is that the description of the incidents does not match the injury.

5. False. Many variables can affect the progression of a bruise. Bruises do tend to follow different stages progressing from red to green, yellow, brown and then clearing. An exact time frame cannot be established when the injury occurred, only that some bruises are older than others.

Chapter XV.1. Diabetes Mellitus
Greg Y. Uramoto, MD

This is a 9 year old boy who has enjoyed his usual state of good health until his polyuria started 2 months ago. He began to lose weight and reported worsening nocturia over this same period. His appetite increased although lately he has more episodes of stomachaches. Today, he had a noticeably sweet smell to his breath and he was breathing faster than usual so his mother brought him to his pediatrician.

Exam: VS T 37.0, RR 44, P 92, BP110/60, oxygen saturation 100% on room air. His weight was 25 kg (25%tile). He is alert and cooperative. His skin is warm to his wrists and ankles. His oral mucous membranes are tacky. His capillary refill is 3 seconds over his chest. His skin was otherwise normal. His thyroid gland is approximately 1.5 times the normal size. His heart rate is regular. He is slightly tachypneic with clear breath sounds. His reflexes are normal. His abdomen has normal bowel sounds has no tenderness. His genitalia and pubic hair are in Tanner stage I. The rest of the physical examination is unremarkable.

His pediatrician suspects new onset diabetes mellitus. A urine dipstick in the office shows 4+ glucose and 2+ ketones. No other dipstick abnormalities are noted. He is clinically stable. He is hospitalized for further management and treatment. His initial lab studies show Na 132, K3.3, Cl 99, bicarb 11, glucose 380, BUN 21, creatinine 0.4. He is started on an IV fluid infusion and subcutaneous insulin.

Prior to the purification of insulin, type 1 diabetes mellitus was uniformly lethal. Although we have made significant strides in the evaluation and management of diabetes, it remains a significant health problem in the general population. In the pediatric subset of the population, type 1 diabetes mellitus is especially challenging since so many factors need to be balanced. The basics on balancing all of these factors will be covered in this chapter.

In United States, the overall risk of developing type 1 diabetes mellitus is 0.2-0.4 percent in Caucasians. In siblings of patients with type 1 diabetes, the risk is approximately 6%. Children of fathers who have type 1 diabetes mellitus have a 6% risk of developing the problem. Children of mothers with type 1 diabetes mellitus have only a 3% chance of developing the problem. The overall incidence of the disease is 18.2 in 100,000/year among people less than 20 years old. The incidence is much higher in Scandinavian countries than in Asian countries.

The National Diabetes Data Group in 1979 divided the heterogeneous condition of diabetes mellitus into two main groups. Type 1 diabetes mellitus has also been called insulin-dependent (IDDM), juvenile onset, ketosis prone, or brittle diabetes. In this type of diabetes mellitus, islet cells are destroyed by an autoimmune process and insulin that these islet cells produce must be replaced. With our current understanding, type 2 diabetes mellitus is primarily an insulin resistant state with a gradual decrease in beta cell function. It was formally known as non insulin-dependent diabetes (NIDDM), adult-onset diabetes, or stable diabetes. Clinical diabetes mellitus can also result from a large number of pathologic processes. Beta cell destruction due to pancreatitis, cystic fibrosis, or surgery can lead to an insulinopenic state that requires insulin injections. Medications including streptozocin, cyclosporin, and corticosteroids can also lead to clinically high blood sugars.

Approximately 2 percent of the American population have some form of diabetes mellitus. Approximately 85 percent of all patients (adults and children) with diabetes mellitus are categorized as type 2. Since type 2 diabetes mellitus is often very subtle, the number of undiagnosed cases of diabetes mellitus is significant. The other 15 percent of patients with diabetes mellitus nationwide are categorized as type 1. In the pediatric population, type 1 diabetes makes up a larger proportion of the cases. Although our estimates are quite crude, some centers report that approximately 98 percent of their children with diabetes have the Type 1 variety. This estimate will certainly be revised in the future as we recognize more type 2 diabetes in children.

Insulin is the primary hormone that suppresses hepatic glucose production, proteolysis, and lipolysis. It is secreted in a biphasic manner in response to glucose. The first phase of insulin release is followed by a nadir and then by a relatively prolonged second phase of insulin release. Catecholamines, cortisol, growth hormone, glucagon, and gastrointestinal hormones among other hormones modulate the insulin response to glucose.

Due to the portal circulation in the gut, blood draining the islet cells of the pancreas goes to the liver before returning to the heart. This portal circulation exposes the liver to an immediately high concentration of insulin soon after a meal. When treating diabetes with exogenously administered insulin into the systemic circulation, we need to remember that this does not duplicate the physiologic state.

Insulin is an anabolic hormone that increases the transport of glucose into cells. With this transport, insulin will decrease the serum glucose. At the cellular level, glucose does not act alone. In reality, the insulin/glucagon ratio is important for determining the body's response to insulin. A high insulin state will induce glucose uptake and inhibit amino acid release in muscle cells. In the liver, insulin will decrease glucose release and decrease ketone body formation. In fat cells, insulin will increase glucose uptake and decrease lipolysis.

In our most current models, type 1 diabetes mellitus is an autoimmune disease. In our current understanding of the problem, people with type 1 diabetes mellitus have an underlying genetic predisposition to developing diabetes. On top of this predisposition, they are exposed to an environmental insult that triggers the immune response. In this way, not everyone who is genetically susceptible to type 1 diabetes mellitus will develop the problem. The identical twin of the patient with type 1 diabetes mellitus has a 25 to 50 percent risk of developing the problem in their lifetime.

Important genes for transmitting this susceptibility to diabetes include the human leukocyte antigens (HLA) that allow for some of the communication between white blood cells. The HLA-DR and HLA-DQ molecules are especially important. These are antigen-presenting structures that T-cells recognize. The antigens in these presenting molecules are the targets for the immune response. Mutations that lead to defects in the structure of this antigen presenting molecule predisposes to type 1 diabetes mellitus. One of the important residues in the structure of the HLA molecules is at position 57. Homozygosity for aspartic acid at this site confers nearly 100% protection against type 1 diabetes. Conversely, a non-aspartic residue at this spot can lead to a nearly 100 fold increase in the incidence of disease.

On top of this genetic predisposition, an environmental insult is likely to be required for the development of diabetes. The environmental factors are quite varied and we are only now beginning to isolate some of them. Congenital rubella cases provide compelling evidence that some of these environmental triggers are viral proteins. Approximately 20 percent of babies with congenital rubella will develop type 1 diabetes mellitus. Most of these cases do not appear until adolescence. Other viruses such as Coxsackie virus, cytomegalovirus, and hepatitis viruses have been implicated.

Polyuria, polydipsia, weight loss, fatigue, polyphagia, anorexia, deteriorating school performance, failure to thrive, and nocturnal enuresis can occur. Clinical symptoms become apparent when the blood sugar rises above the renal threshold and glycosuria induces an

osmotic diuresis. Insulinopenia allows hormone sensitive lipase to cut long fatty-acid chains into two carbon acetate fragments which are converted to ketoacids. Patients will present in varying degrees of decompensation as the serum pH decreases and as the dehydration progresses. New onset type 1 diabetes will frequently present with diabetic ketoacidosis of varying severity.

Secondary enuresis, unexplained weight loss, and polyuria should raise suspicions about diabetes. Testing should include random glucose levels, electrolytes, and ketones. The measurement of hemoglobin A1C and insulin can also be helpful. 90% of children will have elevated anti-insulin, anti-islet cell, or anti-GAD (Glutamic acid dehydrogenase) antibodies. Rarely, an IV or oral glucose tolerance test to evaluate for the degree of insulin-producing capacity may be considered in borderline cases, mostly to confirm type 2 diabetes.

Normal glucose levels should be <126 mg/dl in the fasting state. "Fasting" for this purpose should include no caloric intake for at least 8 hours. A random glucose of >200 mg/dl and elevated ketones in the urine or serum in the presence of classic symptoms of diabetes strongly supports the diagnosis of diabetes.

There is no single test that will definitively differentiate between type 1 and type 2 diabetes. Insulin levels should be high in the presence of high serum glucose levels. At least one of the above antibody tests are usually positive in type 1 diabetes. The clinical course is also helpful in differentiating type 1 and type 2. In the case of type 1 diabetes, the capacity to make insulin will decrease over the course of several months as islet cell destruction advances. In type 2 diabetes, the beta cell function is lost over the course of years to even decades.

Diabetic ketoacidosis (DKA) is a complex subject on its own, beyond the scope of this chapter. DKA occurs in an insulin deficient state when cellular starvation of glucose occurs. Despite hyperglycemia, glucose cannot be transported into many cells in the absence of insulin. Therefore, cellular energy metabolism utilizes lipolysis with resultant organic acid, ketone formation (i.e., ketoacidosis) and visible lipemia (blood samples may appear visibly turbid). Patients classically present with severe dehydration, vomiting, deep respirations (respiratory compensation for metabolic acidosis) and a ketotic odor to the breath. Management begins with IV fluids and insulin (0.1 u/kg) administration. Factitious hyponatremia is present with extreme values of hyperglycemia as seen in DKA. This will correct on its own as the glucose level normalizes. Complications such as cerebral edema may occur, the etiology of which is not fully understood. Fluid administration has not been demonstrated to be the cause of cerebral edema; however caution should be exercised in the rate of administering IV fluids. As a rule of thumb, it may be conservative to infuse normal saline at a rate of LESS than 10 cc/kg/hour (i.e., less than a fluid volume correction of 1% of body's weight per hour). A relatively stable patient can receive fluids at maintenance or 1.5 times maintenance. However, severely dehydrated or patients in shock will need more aggressive fluid administration rates. Cerebral edema occurs because the high extracellular glucose levels result in osmotic gradients which pull water from the cells creating cellular dehydration (similar to how a grape changes into a raisin). At some point, this cellular dehydration results in irreversible cellular injury. A less common phenomenon is known as the hyperosmolar non-ketotic state which is characterized by glucose levels in excess of 1000 mg/dl (DKA glucose levels are typically 300 to 800 mg/dl), little or no ketones (most easily assessed by urine dipstick for ketones), and depressed sensorium or coma. The hyperosmolar non-ketotic state has a substantial mortality rate in the 25% range especially if the patient presents in coma, because cerebral cells are subjected to greater degrees of cellular dehydration and a higher risk of irreversible injury. Why does DKA occur in most patients while the hyperosmolar non-ketotic state occurs in others? The answer is uncertain, but it may have something to do with differences in lipid metabolism between individuals.

Once patients are stabilized on the hospital floor, subcutaneous insulin is currently the standard treatment. This insulin can be delivered with injections or a pump. The back-up system for the pump, however, is injections so everyone should learn the basics of subcutaneous insulin injections.

The key to managing diabetes is to balance the factors that increase the blood sugar with the factors that decrease the blood sugar. The most important of these factors include insulin, diet, and exercise. Parents of children with diabetes need to learn enough about diabetes to take care of their children at home. At the very least, they will need to learn about: insulin injections, the types of insulin, blood glucose monitoring, the influences of diet on blood sugar, the influence of exercise on blood sugar, the influence of illnesses on blood sugar, symptoms of hypoglycemia, and the proper response to high and low blood sugars. Without this basic knowledge, patients cannot be discharged home. Several education sessions are usually needed to cover the large amount of information. With so many important aspects to the treatment of diabetes, a team approach that includes dietitians, counselors, diabetes educators, and doctors usually works best.

The insulin program should be tailored to match the family. The sophistication of the family and the ability of the child to give themselves their own shots are important considerations. Two common insulin programs include the mixed-split program and the multiple daily injection program.

In the mixed split program, two insulin types are mixed together and given in two injections. The two insulin types usually include an intermediate-acting NPH and a short-acting insulin such as Lispro or regular. Each shot is supposed to take care of two different meals so the morning shot will take care of breakfast and lunch. In this way, the child does not need to give a shot in school. This is important if the child is not old enough to give his/her own shots.

The multiple daily injection (MDI) program uses a long-acting insulin like Ultralente or insulin glargine to mimic the physiologic baseline of insulin. On top of this baseline, short acting insulin is given with each meal. This program is fairly flexible and usually leads to better control of the blood sugars.

Insulin doses should be tailored to the patient's needs. One unit per kilogram of insulin per day can be used as a starting dose of insulin in someone who presents in severe DKA. Careful monitoring of the glucose levels is required to adjust the doses on a daily basis while they are in the hospital. Because the insulin shots are not physiologic, we may need to tolerate a high post-prandial sugar in some patients. Some children and infants are continuously post-prandial so their blood sugar control is often quite complex.

The goals of treatment should also be tailored to the family and the patient. Aiming for excessively tight blood sugar control with a complex insulin program will likely fail in children with complex social issues at home. With this in mind long-term management would include getting as many blood sugar levels into a "goal range" as reasonably feasible. A typical goal range for infants and toddlers is between 100 and 200 mg/dl. A typical goal range for 5-11 year old children is between 80 and 180 mg/dl. For older children blood sugars in the normal range are reasonable. Hemoglobin A1C is a measurement of glycosylated hemoglobin. This level reflects the glycemic control over the previous 3 months. Goals for the hemoglobin A1C values should also be tailored to meet the needs of the family and the patient. In general, lower hemoglobin A1C values are desirable, but the incidence of hypoglycemia is important. Hemoglobin A1C values that are less than 8 are often attainable in elementary school children.

To achieve these lower hemoglobin A1 C values, adjusting the insulin doses are mandatory. Most families can learn enough about diabetes to adjust the insulin doses themselves. In the MDI program, trends in the blood sugars that are obtained several hours after the meal-insulin combination can be used to adjust the insulin doses. A consistently high pre-lunch blood sugar, for instance, would imply

that the breakfast insulin should be increased. Other factors that influence the blood sugar should also be considered. The insulin dose should be increased if the meal was not excessive and if the patient was not particularly active.

We are still learning about the pathophysiology of type 2 diabetes. There is some debate about whether insulin resistance or decreased insulin release is the initial problem. Both of these problems occur and the effects of the relative insulinopenia can be found in utero. Adults with type 2 diabetes are much more likely to have had an intrauterine growth retardation than the adults without type 2 diabetes. This is not surprising given the importance of insulin in the growth of fetuses. The early stages of type 2 diabetes are characterized by relatively normal fasting glucose levels but elevated post-prandial blood sugars. This occurs since the insulin that is available can eventually lower the blood sugar levels but cannot take care of the glucose load soon after a meal. As the disease progresses, islet cell function slowly declines in type 2 diabetes and the fasting blood sugars will rise as well.

The treatment of type 2 diabetes can be exactly the same as type 1 diabetes. The same insulin program with the same adjustment strategies will work very well in even the early phases of type 2 diabetes. When type 2 diabetes, as patients slowly lose their ability to make insulin, they will more closely resemble people with type 1 diabetes and insulin becomes a necessity. Before this loss of islet cell function, oral medications can be used. Theoretically, sulfonylureas, biguanides, and thiazolidinediones can be used in children as they can in adults. Studies that show efficacy and safety in children are not yet available so they must be used with caution.

Questions

1. What is a reasonable goal range for infants, children, and teens?
2. Which type of diabetes is primarily an autoimmune problem?
3. The identical twin of a patient with type 1 diabetes has what risk for developing type 1 diabetes?
4. Which antibodies are often present in type 1 diabetes?
5. What is a hemoglobin A1C?
6. In the early phases of type 2 diabetes, is the fasting blood sugar or the postprandial blood sugar elevated?

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Answers to questions

1. Infants: 100-200. Children: 80-180. Teenagers: 70-120.
2. Type 1
3. 50 %
4. Anti islet cell, anti insulin, and anti GAD antibodies
5. HgA1C is the combination of hemoglobin and glucose. It is elevated when the glucose levels are high and it is a good marker for diabetes control.
6. Postprandial.

Chapter XV.2. Thyroid Disorders

Melanie L. Shim, MD

A previously healthy 14 year old female complains of a fast heart rate, weight loss, and fatigue over the past 2 months. Her family history is significant for a grandmother and aunt with Hashimoto thyroiditis.

Exam: VS T 37, HR 110, R 22, BP 120/50. On exam, she is comfortable without diaphoresis. She has a mild tachycardia without murmurs or gallop. She is found to have a smooth goiter with a bruit, a mild tremor, and exaggerated DTRs.

Labs: Elevated T4, undetectable TSH. Thyroid stimulating immunoglobulin assay is positive.

She is diagnosed with Graves' disease. She is treated with PTU (propylthiouracil) after which her thyroid function normalizes. Clinically, there is resolution of her tachycardia, weight loss, and fatigue, and her goiter decreases in size. Her thyroid function is monitored routinely and the dose of PTU adjusted as indicated to maintain a euthyroid state. Two years after diagnosis, she goes into remission and PTU is discontinued.

The hypothalamic-pituitary-thyroid axis regulates production and maintains peripheral concentrations of the biologically active thyroid hormones, thyroxine (T4) and triiodothyronine (T3). Pituitary thyroid stimulating hormone (TSH) secretion is modulated by the stimulatory effect of hypothalamic thyrotropin releasing hormone (TRH) and the inhibitory (negative feedback) effects of T4 and T3 influencing both TRH and TSH secretion. The major secretory product of the thyroid gland is T4. It is synthesized as a component of the large (660-kD) precursor thyroglobulin molecule. Iodine is the rate-limiting substrate, which must be actively transported in to the thyroid follicular cell by a plasma membrane sodium/iodide pump. Iodide trapping, thyroglobulin synthesis, and iodothyronine secretion are all stimulated by TSH. The iodothyronines are transported in blood bound to the thyroid hormone-binding proteins, thyroid hormone-binding globulin (TBG) and transthyretin (prealbumin). Thyroid hormones also bind to albumin and lipoproteins with lesser affinity (1,2).

Only small amounts of T4 and T3 are free or unbound. This free hormone is available to tissues. T4 serves largely as a prohormone and is deiodinated in peripheral tissues by several iodothyronine monodeiodinase enzymes to active T3 or biologically inactive reverse T3 (rT3). The major source of circulating T3 is peripheral conversion from T4, largely by the liver. Only small amounts of T3 are secreted

by the thyroid gland in euthyroid subjects ingesting adequate iodine. Normally, T4 is deiodinated to both T3 and rT3. The T3 mediates the predominant effects of thyroid hormones via binding to the 50-kD nuclear protein receptors, which function as transcription factors modulating thyroid hormone-dependent gene expression (1,2).

During the first trimester of gestation, the thyroid gland arises from the foramen caecum at the base of the tongue and migrates caudally to the neck site. By 12 weeks gestation, iodine trapping and T4 and T3 synthesis occur. Adequate quantities of iodide are essential for fetal thyroid hormone synthesis. The placenta imposes a relative barrier to the thyroid hormones and is impermeable to TSH, so the fetal hypothalamic-pituitary-thyroid system develops largely autonomous of the maternal system. The placenta is permeable to thionamide drugs used to treat maternal hyperthyroidism, which could result in fetal and early postnatal hypothyroidism. In term infants, following delivery, there is a postnatal surge of TSH which returns to normal by 2-3 days. T3 and T4 concentrations increase 2 to 6 fold, peaking at 24 to 36 hours after birth and gradually declining to levels characteristic of infancy over the first 4-5 weeks of life. Normal thyroid function parameters vary with age (1,2).

Thyroid Disorders in Children:

Primary hypothyroidism:

1. Congenital
2. Autoimmune (Hashimoto thyroiditis)
3. Iodine deficiency
4. Iatrogenic (goitrogen ingestion, radiation)
5. Transient (transplacental passage of antithyroid drugs, maternal transfer of antibodies)

Secondary hypothyroidism:

1. Central hypothyroidism (TSH deficiency)

Primary hyperthyroidism:

1. Autoimmune (Graves' disease)
2. Neonatal Graves' disease (transplacental passage of TSH receptor-stimulating antibody)
3. Factitious (ingestion of excess thyroid hormone)

Secondary hyperthyroidism:

1. Hyperthyrotropinemia (TSH excess)

Other thyroid disorders:

1. Thyroid nodules (benign vs. malignant)
2. TBG deficiency or excess
3. Synthetic defects - hormones or carrier proteins
4. Euthyroid Sick Syndrome

Congenital hypothyroidism (3) is an important cause of mental retardation that can be prevented with early identification and treatment. Newborn screening for congenital hypothyroidism is now routine in most industrialized societies. It is based on physiologic principle that primary hypothyroidism results in neonatal TSH hypersecretion. Screening tests are usually carried out with dried blood spot samples collected via skin puncture. In some areas T4 is measured initially, and TSH is measured in samples with the lowest 10-20% of T4 results. In other areas, direct TSH screening has been used. The preferred time for blood sampling is 3-5 days after birth. However, many newborns are now discharged from the hospital before 3 days of age. Early measurement increases the prevalence of infants demonstrating a modest elevation of TSH concentrations due to the physiological neonatal TSH surge; thus increasing the number of false-positive results (4). The prevalence of congenital hypothyroidism approximates 1 in 4000 births. Etiologies include thyroid dysgenesis, thyroid dyshormonogenesis, hypothalamic-pituitary (TSH) deficiency, and transient hypothyroidism (usually iodine, drug, or maternal antibody induced); the proportions approximate 75%, 10%, 5%, and 10%, respectively, of all cases of congenital hypothyroidism.

Thyroid dysgenesis describes infants with ectopic or hypoplastic thyroid glands as well as those with total thyroid agenesis. It is usually sporadic, with a 2:1 female preponderance. Ectopic glands may be located anywhere from the base of the tongue, along the thyroglossal duct, laterally, or as distant as the myocardium. A normal or near normal circulating level of T3 in the presence of low T4 suggests the presence of residual thyroid tissue, and this can be confirmed by a thyroid scan. A measurable level of serum thyroglobulin indicates the presence of some thyroid tissue; athyroid infants have no circulating thyroglobulin.

Dyshormonogenesis, or the inborn errors of thyroid hormone synthesis, secretion, and utilization, follows an autosomal recessive pattern of inheritance. The most common defect involves deficiency of thyroperoxidase enzyme, which is responsible for organification of iodide. When present with sensorineural hearing loss it is known as Pendred syndrome. Other defects may involve iodide trapping, coupling of tyrosyl rings, abnormal thyroglobulin synthesis, or deiodination of iodothyronines.

Transient congenital hypothyroidism may result from goitrogenic agents and transplacentally derived TSH receptor-blocking maternal autoantibodies. The presence of a goiter in an infant is supportive evidence of antithyroid drug- or goitrogen- induced transient hypothyroidism. Maternal TSH receptor-blocking antibody-induced hypothyroidism should be suspected in any case in which the mother has a history of autoimmune thyroid disease. The presence in maternal or neonatal blood of a high level of TSH receptor-blocking antibody is strong supportive evidence.

Confirmatory diagnosis of congenital primary hypothyroidism is based on measurement of T4 (low) and TSH (high). Optional studies include ultrasound and radionucleotide scan. Physical examination may reveal one of several early and subtle manifestations of hypothyroidism, including a large posterior fontanelle, prolonged jaundice, macroglossia, hoarse cry, distended abdomen, umbilical hernia, hypotonia or goiter. Fewer than 5% of infants are diagnosed on clinical grounds before the screening report, but 15-20% of infants have suggestive signs when carefully examined at age 4-6 weeks, after the screening results have been reported. For infants with congenital hypothyroidism, prompt initiation of levo-thyroxine (75-100-ug/m2/d) treatment is essential. Delayed institution of treatment (>45days) is clearly associated with diminished mean IQ.

Hashimoto thyroiditis (autoimmune hypothyroidism, chronic lymphocytic thyroiditis) is an autoimmune, inflammatory process causing 55-65% of all euthyroid goiters and nearly all cases of hypothyroidism in childhood and adolescence (5,6). Prevalence studies have found that as many as 1.2% of school-aged children have chronic lymphocytic thyroiditis as defined by an enlarged thyroid gland and detectable thyroid antibodies in the serum. Females predominate at a ratio of 2:1 with a peak age of onset in mid-puberty. It is rare under 4 years of age. The specific mode of inheritance is not known, but there is a high familial incidence. Thyroid inflammation and damage result from self-directed humoral and cell-mediated immunity. Antibody markers of the destructive process include anti-thyroglobulin and anti-thyroperoxidase antibodies. One or both of these antibodies are present in virtually all patients with chronic lymphocytic thyroiditis, but they are not specific for this disorder and may be found in other autoimmune diseases such as Graves' disease, Addison's disease, and Type 1 diabetes.

The initial presentation of Hashimoto thyroiditis can usually be categorized as thyromegaly with euthyroidism, toxic thyroiditis, or hypothyroidism with or without thyromegaly. The majority of patients are asymptomatic and present with an enlarged thyroid gland. The gland may be symmetrically or asymmetrically enlarged with a bosselated (cobblestone) texture. Toxic thyroiditis (Hashitoxicosis) is a transient, self-limited form of hyperthyroidism occurring in less than 5% of patients. If hypothyroidism is present, there may be a history of poor growth, fatigue, constipation, mild weight gain, dry skin and cold intolerance.

The initial screening of thyroid function should include measurement of serum free T4, TSH, and anti-thyroid antibodies. Again, most children are euthyroid initially (normal T4 and TSH). The incidence of hypothyroidism (low T4 and high TSH) is 3-13% and compensated hypothyroidism (normal T4 and high TSH, signifying possible impending hypothyroidism) occurs in up to 35%. In addition, serum T3 concentration should be determined if the patient appears to have hyperthyroidism.

Treatment involves replacement with levo-thyroxine (50-100 ug/m2/d) to normalize TSH and T4. Long-term follow-up studies indicated that chronic lymphocytic thyroiditis resolves in 50% of children. Replacement therapy should continue until the patient has achieved final adult height. At that time, a trial without medication may be considered. If a child has positive antibodies but is euthyroid, replacement therapy is not necessary, however thyroid function should be monitored regularly. Children with transient toxic thyroiditis can be treated with propranolol.

Graves' disease (autoimmune hyperthyroidism) is the autonomous production of excessive thyroid hormones by a usually enlarged thyroid gland that is not under pituitary control (7,8,9). It is the most common cause of hyperthyroidism in children. There is a high familial incidence, and females predominate in a 3:1 ratio. The peak incidence occurs during adolescence.

Graves' disease arises from autoimmune processes, which include production of immunoglobulins against antigens in thyroid, orbital tissues, and dermis. Thyroid-stimulating immunoglobulins (TSI) are present in nearly all patients. These antibodies bind to the TSH receptors on the thyroid cells and have a stimulatory (TSH-like) effect. TSI, like TSH, stimulates thyroid follicular cell growth to cause thyromegaly. Anti-thyroglobulin and anti-thyroperoxidase antibodies are also found in many patients, but in lower levels than in Hashimoto thyroiditis. Graves' disease and Hashimoto thyroiditis may in fact be a part of a spectrum of the same disease process.

The sustained state of an increased metabolic rate results in enhanced energy expenditure to cause a catabolic state. Clinical features include nervousness, irritability, palpitations, tachycardia, tremor, increased appetite with weight loss, diarrhea, difficulty sleeping, heat intolerance, poor school performance, irregular periods, and rapid height velocity. Most patients will have a goiter. Even though up to 50% of children with Graves disease manifest ophthalmopathy, this problem is not as severe as in adults. Lid retraction and stare are the most common, whereas chemosis (conjunctival swelling), lid eversion, and paresis of extraocular muscles are found predominately in adults. Graves dermopathy (pretibial myxedema) in children is virtually nonexistent.

The thyroid hormone profile characteristically shows elevated T4 and T3 levels, accompanied by very low or undetectable levels of TSH. In 15-20% of cases, the T3 level is elevated with a normal level of T4 (T3 toxicosis). This represents an early stage of thyrotoxicosis, prior to the elevation of T4.

The three forms of treatment for Graves' disease are medical, surgical, and radioactive iodine ablation. The mainstay of medical management is antithyroid mediations with methimazole or propylthiouracil. Both are equally effective at decreasing the production of T4 and T3 by the thyroid gland, but propylthiouracil also blocks the peripheral deiodination of T4 to T3. Side effects are infrequent, but include skin rashes, arthritis, hepatitis and agranulocytosis. Evidence suggests that with antithyroid medication alone, remission of Graves' disease (defined as being euthyroid for 1 year after stopping medications), occurs at a rate of 25% over 2 years. If medical treatment must be discontinued because of side effects, frequent relapses, or inability of comply with the treatment schedule, thyroid ablative therapy or thyroidectomy should be implemented (10).

Thyroid cancer in children (11). There is about a 30% chance that a nodule found in a child will be malignant. In children who have had other forms of cancer there is a 50-fold increased risk of thyroid cancer secondary to the use of radiation therapy. Basic thyroid function tests are usually normal. Thyroid scans using 123I or 99m Tc-pertechnetate are helpful in the evaluation of a thyroid nodule. A "cold" area (hypofunctioning) on scan increases the suspicion of malignancy while "hot" (hyperfunctioning) nodules are almost invariably benign. Needle biopsy is the most simple and direct method to help determine the architecture of a thyroid nodule.

Papillary cancer is the most common malignant thyroid tumor in children (60-80%). These tumors often consist of a mixture of papillary and follicular elements. Pure follicular carcinomas comprise about 10-15% of cases (12). Medullary carcinomas account for less than 7% of all thyroid cancers and may be sporadic, familial (autosomal dominant), or part of one of the multiple endocrine neoplasia syndromes. Malignant or suspicious lesions require surgical intervention and post-operative ablation with 131I followed by appropriate surveillance.

Questions

1. True/False: The major secretory product of the thyroid gland is T3.
2. True/False: A low T4 and low TSH at newborn screening suggests thyroid dysgenesis.
3. True/False: Most patients with Hashimoto thyroiditis present with a goiter and are asymptomatic.
4. True/False: Graves' ophthalmopathy is more severe in children than in adults.
5. True/False: Graves' disease occurs equally among males and females.
6. True/False: Papillary carcinoma is the most common type of thyroid cancer in children.

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Answers to questions

1.F, 2.F, 3.T, 4.F, 5.F, 6.T

Chapter XV.3. Short Stature

Maureen M. Petersen, MD
Anita M. Pedersen, MD

A 10 year old girl presents to your clinic for evaluation of short stature. Parents report that she has always been the shortest girl in her class, but they have become concerned because the patient's 8 year old sister is now the same height as she is. The patient has not yet attained menarche and her mother reports no breast development. She has been well with no chronic medical problems, no hospitalizations, and no surgeries. She lives with her mother, father, and sister and she is currently a straight A student in the fifth grade. Her mother is 173 cm (5'8") and weighs 68 kg (150 pounds). She had menarche at age 12. The patient's father is 185 cm (6'1") and weighs 95 kg (210 pounds). He started shaving at age 15. There is no family history of any medical problems. On further history, you find that your patient was 43 cm (17 inches) long at term (average is 49.5 cm, 19.5 inches).

Exam: VS T 37.0, P 90, R 18, BP 100/60. Height 120 cm (<5%), weight 23 kg (slightly <5%). She is an alert, small appearing girl who is in no apparent distress. HEENT exam is normal. Neck is supple with webbed appearance. Heart regular rate, no murmurs. Lungs are clear. Abdomen is soft without masses. Tanner 1 breasts with wide-spaced nipples are evident. The carrying angle is increased. Tanner 1 pubic hair is noted.

Her growth chart is reviewed which demonstrates an average growth velocity of 3 cm per year. She is sent for a bone age that is read by the pediatric radiologist as 8 years and 6 months. CBC, ESR, TFT's, UA, and serum electrolytes are normal. Chromosomes are obtained revealing a 45XO pattern. The diagnosis of Turner Syndrome is made. You refer her for a renal ultrasound, cardiology evaluation, and a hearing screen. She is also seen by the pediatric endocrinologist and is started on growth hormone.

Growth is an important task for infants and children to accomplish. Short stature is a common pediatric problem with potential long-term sequelae if a pathologic cause remains undiagnosed. Physicians though, can be reassured that the majority of cases of short stature have a nonpathologic cause and by obtaining a thorough history, physical exam, and screening tests, short stature can be readily evaluated.

Growth is primarily controlled by the hypothalamus and pituitary gland. The pituitary gland has two lobes, the anterior lobe (adenohypophysis) and the posterior lobe (neurohypophysis). Growth hormone is secreted in a pulsatile fashion from the anterior lobe of the pituitary in response to two hypothalamic hormones, GH-releasing hormone (GHRH) and somatostatin. GHRH stimulates and somatostatin inhibits the secretion of growth hormone. GH stimulates the production of insulin-like growth factors (IGFs), especially IGF-1, mainly in the liver. These proteins then circulate and stimulate tissues to grow. GH can also directly act on growth plates to stimulate growth. IGF-1 and GH then feed back to the hypothalamus to inhibit secretion of GHRH and stimulate secretion of somatostatin.

Obtaining a complete and precise history in the work-up of a short child is crucial. It is important to inquire about prenatal history, gestational age at birth, weight and length at birth, and neonatal medical history. Adjustments must be made when plotting the weight, height, and head circumference of a former premature infant. In general, weight, height, and head circumference should be corrected until the child is about 24 months of age, unless the child's birthweight was less than 1500 grams in which case, correction until three years of age is recommended. Healthy, premature infants do display catch-up growth. Term infants can have intrauterine growth retardation (IUGR) that can affect the infant's weight, length, and even head circumference. Many causes of IUGR have been identified, including pregnancy-induced hypertension and maternal infections. Potential for future growth in infants with IUGR is variable and depends on the etiology. A neonatal history that includes hypoglycemia, prolonged jaundice, or microphallus should raise suspicions of hypopituitarism. Midline defects such as cleft palate may also be associated with panhypopituitarism or specific deficits in growth hormone or thyroid hormone production.

The medical history should also include the patient's past medical problems and current medications. Long-term corticosteroids, like those used in the treatment of asthma, can affect a child's height. Catch-up growth can be seen when the medication is discontinued, but this is also dependent on the underlying disease. Children with ADHD who are treated with stimulants are at risk of growth

retardation. There often is a noticeable growth spurt when the medication is discontinued. Gastrointestinal, renal, hematologic, or cardiopulmonary disease can cause growth failure. In a patient with Crohn's or celiac disease, linear growth failure may even be the presenting complaint.

The family history is important information that can aid in determining potential reasons for short stature, as well as the child's expected height. One measure that is used for comparison is the adjusted mid-parental height (AMPH). The AMPH in a girl is the average of the father's height minus 13 cm and the mother's height. The AMPH in a boy is the average of the mother's height plus 13 cm and the father's height. Most children achieve their AMPH within approximately 5 cm. The two most common reasons for short stature in otherwise healthy children are familial short stature and constitutional delay. In both conditions, children are normal size at birth, but gradually fall across growth percentiles to resume a normal growth velocity at or below the bottom of the linear growth curve by age two or three. A short child with a normal growth velocity and a less than average mid-parental height can be diagnosed with familial short stature. Parents should also be asked when they entered puberty. A family history of delayed puberty in a short child with a normal growth velocity can help make the diagnosis of constitutional delay of growth and puberty, which means that the child is likely to enter puberty later than his/her peers and finish growing later, ending up with a height that is roughly normal.

A thorough physical exam should be completed on a child with short stature. Time should be spent obtaining accurate growth measurements. Weight, height, and head circumference should be plotted on the appropriate chart. A length (supine measurement) should be plotted on an infant (0-36 month) growth chart. A standing height should be plotted on a growth chart for children 2-18 years. Using prior height measurements, the child's growth velocity should be calculated. A clinician should become concerned if a child's growth velocity is less than 5 cm per year between the ages of 4-10 years. A height age can be determined by drawing a horizontal line from the patient's height to the 50th percentile line for height and then dropping a vertical line to the baseline to determine the height-equivalent age. Arm span should be measured and the upper-to-lower extremity ratio (pubis to crown of head compared to pubis to floor measurements) should be calculated. If these are abnormal, a skeletal dysplasia such as hypochondroplasia should be contemplated and evaluated with further x-rays. Determining a child's weight-to-height ratio also has some diagnostic value. In a child with short stature secondary to endocrine pathology, the child's weight will continue to progress normally or even increase relative to his or her height. Physical characteristics that might indicate a short statured syndrome should be sought. Turner Syndrome, for instance is associated with short stature, and stigmata on physical exam can include webbed neck, low posterior hairline, edema of the hands and feet, and wide-spaced nipples. Of note, these findings may be subtle or even absent in a girl with Turner Syndrome. Chromosomes should be obtained if Turner Syndrome is suspected or if all other causes of growth failure are ruled out in a short girl. A complete physical exam in a short child might detect a heart murmur that could lead a clinician to the diagnosis of significant cardiovascular disease, which can affect a patient's height, or an enlarged thyroid gland, which might indicate hypothyroidism-induced growth failure. (Hypothyroidism can, however, be present with a normal thyroid exam.)

Growth hormone deficiency is a pathologic cause of short stature that should be suspected in a boy with micropenis or any child with a midline abnormality (e.g., cleft palate, septo-optic dysplasia, or holoprosencephaly). Physical findings may also include a childlike appearance (excess fat relative to lean mass) and excess downy hair on the back.

Following a complete history and physical exam, a clinician can use ancillary tests to screen for potential causes of a child's short stature. A bone age can help determine a child's skeletal maturation. This test is performed by obtaining a radiograph of a child's left hand and wrist. The epiphyseal centers seen on the radiograph are compared to age-appropriate standards to determine a bone age. In children less than 2 years, a hemiskeleton bone age should be obtained. This test is performed by obtaining radiographs of the child's entire left upper and lower extremity. The number of ossification centers is determined and again compared to age-appropriate standards to determine the bone age. It is very helpful in the classification of short stature to compare chronologic age, bone age, and height age. In familial short stature, the patient's chronologic age and bone age are equivalent and both are older than the patient's height age. In constitutional delay and malnutrition, the patient's bone age and height age are equivalent and both are younger than the patient's chronologic age. A patient with hypothyroidism can present with a chronologic age older than height age, and bone age much younger than both.

Commonly, thyroid function tests (free T4 and TSH), a complete chemistry profile to include LFT's, a urinalysis and urine culture, and a CBC with ESR are carried out to look for occult causes of poor growth. In the child with delayed bone age and poor linear growth velocity but normal weight, low serum IGF-1 and IGF-BP3 (insulin-like growth factor and IGF binding protein 3) measurements may give clues to the presence of growth hormone deficiency. These patients should be referred to a pediatric endocrinologist for further testing. Random determination of serum growth hormone is not useful. Growth hormone stimulation tests are generally carried out by endocrinologists using agents which cause growth hormone release (e.g., insulin, arginine, L-dopa, clonidine) to determine "provocative" growth hormone levels which are more diagnostic.

A child's growth hormone secretory capacity is not always clear, even after extensive evaluation and testing. If growth hormone deficiency is suspected, a six to twelve month trial of growth hormone therapy may be carried out after an MRI of the sella is obtained. Recombinant growth hormone has been available since 1985 and there are numerous completed and ongoing studies attempting to evaluate its effectiveness in many different clinical settings. Short stature alone is not sufficient criteria to begin a child on growth hormone, as it is not only expensive and not without serious potential side effects, but also there may be no ultimate height benefit. Outside of accepted indications, e.g., GH deficiency, Turner Syndrome, and chronic renal failure, GH should only be administered in a research setting. Recently, GH has been gaining acceptance as an intervention in Prader Willi Syndrome and in some cases of IUGR.

In summary, short stature is a complaint that pediatricians commonly encounter in the outpatient setting. The key to diagnosing a cause is a detailed history, thorough physical exam, and meticulous height measurements over time. Ancillary tests can be of benefit, but a differential diagnosis should be contemplated prior to ordering additional information. The therapeutic goal is to allow children to grow as tall as their genetic potential.

Questions

1. What is the AMPH of a girl whose mother is 175 cm (5'9") and father is 193 cm (6'4")?
2. A) How should height be measured on a 22 month old boy? B) How should height be measured on a 39 month old girl?
3. You are evaluating a boy with a height below the 5% for age and weight is at the 50% for age. You are concerned that his growth is secondary to an endocrine cause. Should you order a serum growth hormone level in your work-up?
4. How do you obtain a bone age on a 20 month old child?
5. What is the cause of short stature in a 14 year old boy with a normal growth velocity and Tanner 2 genitalia on physical exam?

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Answers to questions
1. 177.5 cm (5'10")
2. A) supine B) standing
3. No, random serum growth hormone levels are generally unhelpful in the work-up of short stature.
4. hemiskeleton
5. constitutional delay of growth and adolescence

Chapter XV.4. Adrenal Disorders
Jose L. Gonzalez, MD, MSEd, JD

Case 1: A 17 year old single mom brings her first born one week old male infant to your office with a chief complaint of not feeding well. He is described as having one episode of vomiting yesterday and 2 episodes of spitting up with poor feeding today. There is no history of fever, diarrhea or coughing. His urine output is decreased. Perinatal history is positive only for an inconsistent prenatal care. He was born at term weight 3.2 kg. Family history is negative.

Exam: VS are all normal. Weight is 3.0 kg; length is at the 25th percentile. He is sleepy but arousable. When awake, he appears irritable, failing to be consoled by sucking on a pacifier. The anterior fontanel is somewhat sunken but the conjunctivae and the oral mucosa are both moist. Cardiac exam is positive only for a borderline tachycardia. There are no murmurs or extra heart sounds. His abdomen is soft and negative. Genitalia are prepubertal and adequately developed. Both testes are descended. His neurological exam is non-focal and physiologic except as described above. His skin is clear with good turgor and his capillary refill is 3 seconds.

Lab: Na 128, K 6.9, Cl 98, bicarb 18. Blood sugar 70. CBC is unremarkable except for evidence of hemoconcentration. Urinalysis is negative with a specific gravity of 1.025. Lumbar puncture reveals clear fluid with no cells or bacteria on gram stain. CSF glucose is 33, protein 45. A urine Na is ordered and this shows an inappropriately high urine Na of 50. A tentative diagnosis of salt wasting due to adrenal insufficiency and probable congenital adrenal hyperplasia is made. An EKG is normal except for slightly prominent T waves.

The infant is started on IV hydration with D5NS (without potassium). His clinical hydration status improves markedly after a total of 30 cc/kg is infused. After obtaining advice from an endocrinologist, additional blood studies are drawn and the infant is given IV hydrocortisone. A repeat chemistry panel 4 hours later shows a Na 134, K 5.2, Cl 98, bicarb 18, glucose 80.

Case 2: A nine year old female is brought to your office by her parents with a chief complaint of thickened nails. The thickened nails have been present for over six months and have not responded to topical ointments. Two visits to a podiatrist also failed to clear the problem although the nails did temporally improve after filing. She is now increasingly distressed because of an upcoming hula presentation (in her bare feet).

Her past medical history is negative. Review of systems is positive for a tanned complexion (even with only average sun exposure) and for intermittent complaints of lower leg cramps. The leg cramps are, at times, quite painful but resolve spontaneously after 1 to 2 minutes with rest and massage. They occur randomly without an association to increased exercise and were diagnosed by a local practitioner last year as growing pains. Family history shows that both parents are Swedish born, having migrated to the United States just shortly before the patient's birth. There is an older sister, aged 16 years, quite tall and post-menarchal. Her parents and sister have a fair skin complexion. There has been no recent travel.

Exam: VS T37, P80, R25, BP 90/70. Height and weight are both at the 50th percentile. HEENT, cardiac, pulmonary and abdominal exams are non-contributory. Breasts and genitalia are Tanner stage I. Neurological evaluation is physiologic and non-focal. Her complexion is well tanned even in areas that are not sun exposed. Her nails are thickened and brittle (8 of the 10 toenails and 4 of the 10 fingernails) consistent with a fungal process. The nails are not upturning.

Addison's disease is suspected on the basis of the tanned complexion and the onychomycosis. A serum cortisol level is low and an ACTH level is high. Treatment with oral hydrocortisone replacement is initiated.

The adrenal gland is basically composed of a cortex and medulla. The cortex produces glucocorticoids, mineralocorticoids (also known as mineralocorticoids), and small amounts of sex steroids (progestins, androgens). Excess glucocorticoids may result in hyperglycemia and symptoms and signs of Cushing's syndrome. Mineralocorticoid excess results in excess sodium retention and potassium depletion. Deficiencies of glucocorticoids and mineralocorticoids result in the opposite conditions. The adrenal medulla produces catecholamines. Adrenal disorders result when the production of any of these hormones is insufficient or in excess.

Adrenocortical insufficiency in pediatric patients is principally the result of two distinct pathophysiologic processes. The first type, and by far the most common in infants, is the salt-losing form of congenital adrenal hyperplasia (CAH) (see first case above). Approximately 95% of CAH is secondary to an inherited, autosomal recessive deficiency of the 21-hydroxylase adrenal enzyme (21-OHase CAH). Less frequent etiologic enzyme defects include deficiencies of 11-OHase and 17-OHase, both associated with hypertension as a result of the abnormal accumulation of adrenal precursor hormones with weak mineralocorticoid activity. The second type of adrenal

insufficiency in pediatrics is acquired, typically idiopathic and presents during childhood and adolescence (see second case above). Addison's disease classically refers to idiopathic acquired adrenal insufficiency, but autoimmune and other acquired conditions resulting in adrenal insufficiency are often also referred to as Addison's disease. Less common causes of primary adrenal insufficiency include congenital adrenal hypoplasia (as opposed to hyperplasia), fulminant sepsis, adrenal hemorrhage from various etiologies, inadequate replacement of adrenocortical hormones after surgical removal of adrenal neoplasms, and inappropriate tapering of corticosteroids in children who have received long-term, high dose adrenal glucocorticoid therapy. Additionally, rare forms of adrenal insufficiency result secondarily from a primary ACTH deficiency associated with various pathologic conditions of the hypothalamic-pituitary region.

Infants with 21-OHase CAH classically present with clinical virilization (obvious in females, much less obvious in males), hypotension and mild hypoglycemia from cortisol deficiency, and an associated aldosterone deficiency with a resultant sodium depletion and hyperkalemia. Although the exact pathophysiology for the lack of a normal aldosterone effect is still debatable, the resulting salt-wasting abnormalities can lead to severe life-threatening hyperkalemia, hyponatremia and acidosis. Approximately two-thirds of children with classical 21-hydroxylase deficiency will present clinically with the salt-losing form within the first 2 to 3 weeks of life. A rare condition that may mimic salt-losing congenital adrenal hyperplasia, and which must be considered in the differential diagnosis is pseudohypoaldosteronism. This "functional" aldosterone disorder is caused by a defect at the aldosterone receptor site. Although similarly hyponatremic and hyperkalemic, these latter patients, unlike 21-OHase CAH infants, are not virilized and display contrastingly elevated aldosterone levels and usually normal, or only mildly stress-increased adrenal androgen concentrations (e.g. 17-hydroxyprogesterone, androstenedione and DHEA-S).

Congenital, virilizing, 21-hydroxylase deficiency may be either salt wasting or non-salt-wasting. Infants with the salt-losing type are easier to diagnose and will present to medical attention sooner. Alternatively, infants, especially males, with the non-salt-losing type may be difficult to diagnose since they lack the typical electrolyte abnormalities of salt-losers and may remain unrecognized for years until clinical signs of excess early virilization become evident.

The basic biochemical pathway within the adrenal cortex converts cholesterol to aldosterone, cortisol and adrenal androgens. ACTH stimulates this pathway and the production of cortisol provides negative feedback to reduce ACTH stimulation. The 21-hydroxylase enzyme is required to convert precursors to both cortisol and aldosterone. In salt-wasting 21-hydroxylase CAH, cortisol production is deficient resulting in high ACTH levels. Similarly, the resultant aldosterone deficiency leads to elevated levels of plasma renin. In the non-salt-wasting variety of CAH, the aldosterone pathway remains intact, although renin levels may be inappropriately elevated, suggesting an inefficient mineralocorticoid production. In both CAH types, however, the elevated ACTH stimulates the adrenal cortex's biochemical pathway. This causes shunting of hormone production away from cortisol towards an excess accumulation of various androgenic precursors, such as 17-OH progesterone and androstenedione that lead to the evident virilization.

The usual infant with the salt-losing form of congenital adrenal hyperplasia will present with dehydration and signs of both acute and chronic hypovolemia, with or without peripheral vascular collapse, sometime between the third and 28th day of life. Such signs, however, may appear under uncommon circumstances as late as three to four months of age (e.g., premature infants receiving supportive salt-containing intravenous fluids). Male infants with salt-losing, virilizing CAH tend to have subjectively normal external genitalia at birth. In contrast, female babies with this condition will characteristically demonstrate virilized ambiguous external genitalia at delivery from a prolonged intrauterine exposure to excessive adrenal androgens; a dysfunctional response maintained by the absence of a negative pituitary ACTH feedback effect from the underlying primary cortisol deficiency. Although a disease with autosomal recessive inheritance, prior collected data has documented an unexpected majority (greater than 60%) of CAH female infants, suggesting that a substantial number of male infants with congenital adrenal hyperplasia remain undiagnosed. More recent studies based on newborn screening data, however, have revealed more predictable gender proportions, thus supporting the value-added benefits of such a prevention strategy of newborn screening for treatable metabolic defects.

Analysis of now available genetic information indicates that the genetic mutations leading to congenital adrenal hyperplasia have been mapped to the class III region of the HLA complex (specifically HLA-B and HLA-DR) located on chromosome six. Subsequent work by the pediatric endocrinology group at Cornell has successfully defined the precise 21-OHase gene structure. These investigations have shown that CAH patients with classic 21-hydroxylase deficiency, with and without clinical salt loss, have a similar genetic abnormality. Alternatively, although located at the same genetic locus, patients with the other non-classical, virilizing forms of 21-OHase CAH, carry a different and distinct allelic abnormality, a genetic pattern analogous to that seen with hemoglobin S and C diseases.

The diagnosis of CAH is established by laboratory findings of a low cortisol in the presence of elevated levels of ACTH and adrenal androgens, the latter either obtained randomly or after stimulation with ACTH. Patients with the salt-wasting form will additionally demonstrate laboratory evidence of hyponatremia and hyperkalemia in association with a suppressed aldosterone concentration and an elevated plasma renin activity. A simple test to demonstrate inappropriate salt wasting from aldosterone deficiency is to obtain a urine sodium measurement when the patient is hyponatremic. In contrast to the expected findings of appropriately low urine sodium in the setting of hyponatremia, the urine sodium in salt wasting states such as mineralocorticoid deficiency or resistance will be inappropriately high.

In the not too distant past, infection-associated causes of acquired adrenal insufficiency predominated and included, most commonly, tuberculosis and fulminant bacterial sepsis. Today, however, acquired, idiopathic adrenal insufficiency occurs principally as a result of an autoimmune destruction of the adrenal gland. Autoimmune Addison's disease may occur either as an isolated phenomenon or, more commonly, as part of a more generalized, autosomal dominant polyglandular autoimmune failure syndrome. Given the often subtle clinical symptoms of acquired primary adrenal insufficiency, most patients with the polyglandular failure syndrome, if Type I, present characteristically with complaints of recurrent oral thrush and chronic ungual candidiasis from the underlying T-cell immune dysfunction. Both finger and toe nails can be affected with findings of opaque, thickened, friable and brittle nails. The polyglandular failure syndrome itself occurs in two types and typically consists of the following constellations of endocrinopathies:

Type I	Type II
Hypoparathyroidism (90 %)	Addison's disease (100 %)
Addison's disease (60 %)	Autoimmune thyroid disease (70 %)
Hypogonadism (45 %)	Insulin-dependent diabetes (50 %)
Mucocutaneous candidiasis (75 %)	Hypogonadism (10 %)
Autoimmune thyroid disease (10 %)	Vitiligo (5 %)

Acquired adrenal insufficiency can also commonly occur from an iatrogenic suppression of the hypothalamic-pituitary-adrenal axis. Given the widespread use of corticosteroids as therapeutic anti-inflammatory agents in the treatment of such conditions as asthma, arthritis or as adjunctive chemotherapy, iatrogenic adrenal insufficiency is at present, probably the number one etiology of adrenal cortisol deficiency. Supraphysiologic dosages of exogenous corticosteroids for periods as short as 4 weeks have been associated with the prolonged (up to one year!) inhibition of ACTH-mediated cortisol production.

Even when temporally associated with an acute event (e.g., adrenal hemorrhage from sepsis-associated disseminated intravascular coagulation), the clinical presentation of acquired adrenal insufficiency is typically insidious as well as nonspecific in its symptomatology. Unless the health care provider carries a high index of suspicion, suggestive clinical symptoms of lethargy and easy fatigability and physical signs of postural hypotension and fasting hypoglycemia in at-risk patients will surely be missed. In patients with primary cortisol deficiency, and thus with elevated ACTH levels, the presence of a generalized bronzing ("tanning") of the skin from an excess ACTH effect can be diagnostically helpful in supporting the laboratory evaluation for a suspected adrenal insufficiency. With in-vitro findings of ACTH receptors in melanocytes, it is believed that the increased tanning of the skin results from excess melanin deposition in the dermis.

Patients with acute adrenal insufficiency may present with both hypothermia and shock from peripheral vascular collapse. Vital signs including systemic arterial blood pressure, heart rate, respiratory rate and temperature must be monitored hourly until stable. In addition, the ECG must also be monitored continuously since hyperkalemia can cause severe ventricular dysrhythmias. Patients who do not respond to the initial fluid challenges with an increase in systemic arterial blood pressure, peripheral perfusion and urinary output require a central venous catheter for appropriate monitoring of central venous blood pressure.

Serum electrolytes (Na, K, C1, and HCO3) must be obtained immediately upon admission and followed at 4 hour intervals for the first 24 hours of management. Prior to the start of therapy in infants, blood must also be obtained for ACTH, androstenedione, 17-hydroxyprogesterone (17-OHP) and plasma renin studies. The 17-OHP serum assay has been shown to be a dependable and reliable diagnostic technique in infants with congenital adrenal hyperplasia, even when acutely ill. Collection of 24 hour urine for determination of 17-hydroxycorticosteroids (17OHCS), reflecting blood levels of glucocorticoids, or 17-ketosteroids, the standard diagnostic test for evaluating adrenal androgen excretion in the past, is not presently considered practical in young children and much less so in those with vascular instability. In older children who present with primary adrenal insufficiency, a blood sample for determination of serum cortisol and ACTH levels must be similarly obtained prior to the initiation of steroid therapy. In patients with primary adrenal insufficiency, the cortisol level will be low, whereas the ACTH level will be substantially elevated as a result of an absent, negative pituitary feedback mechanism. Although optimal, dynamic studies such as ACTH stimulation tests should be avoided if they, in any way, compromise the patient's clinical status.

The aim of endocrine treatment is to replace the deficient adrenal steroids. Acute fluid therapy must be continued until hormonal replacement is, by itself sufficient to sustain the patient's clinical stability.

For glucocorticoid replacement, an initial bolus of glucocorticoids, such as hydrocortisone sodium succinate, or its therapeutic equivalent (See table 1), must be administered intravenously at a bolus dose of 60 to 80 mg per square meter (body surface area). Initial dosages less than 25 mg in an infant or greater than 100 mg in an older child should be avoided. The initial bolus of glucocorticoids should be repeated if there is an inadequate clinical response to treatment as judged by systemic arterial blood pressure, peripheral perfusion, and urine output. Intramuscular cortisone acetate (60 mg per square meter of body surface area) may be administered as a repository dose of glucocorticoid at the same time as the initial bolus treatment. The half-life of cortisone acetate is approximately 24 hours and its duration of action may last up to 2 to 3 days.

As soon as a pattern of clinical improvement has been established, one-third to one-half of the initial dose of intravenous hydrocortisone sodium succinate must be continued every 4 hours for the subsequent 24 hours, by which time effective glucocorticoid replacement should be complete. The half-life of hydrocortisone sodium succinate is approximately 60 to 90 minutes and its duration of action is about 4 hours. Upon effective completion of glucocorticoid replacement, and provided the patient's clinical status permits, the patient may then be switched to oral maintenance therapy with hydrocortisone at 15 mg per square meter per day divided into three equal doses, a dosage intended to approximate the physiologic daily secretory rate of cortisol, 12 mg per square meter of body surface area.

If adrenal insufficiency is severe at presentation, a regimen of intramuscular cortisone acetate 30 mg per square meter given every 12 hours should be continued for an additional 24 to 48 hours before changing to oral hydrocortisone maintenance.

Table 1 - Glucocorticoid Potency Equivalency

Cortisone	25 mg (least potent)
Hydrocortisone	20 mg
Prednisone	5 mg
Prednisolone	5 mg
Methylprednisolone	4 mg
Dexamethasone	0.75 mg (most potent)

For mineralocorticoid replacement, parenteral mineralocorticoid therapy as intramuscular aqueous deoxycorticosterone acetate (DOCA) has been unavailable for close to 10 years. Current recommendations for salt-wasting CAH patients presenting with hyponatremia and/or hyperkalemia consist of oral fludrocortisone acetate (Florinef), 0.05 to 0.2 mg/day given b.i.d. or as a single daily dose, started as soon as the patient is able to retain oral fluids. Unfortunately, although Florinef is an effective medication for long-term maintenance therapy, the acute biochemical mineralocorticoid effects of oral fludrocortisone acetate may be delayed by 48 to 72 hours. Until then, the continued infusion of salt containing intravenous solutions will be needed to correct the hyponatremia and hyperkalemia seen with salt-losing adrenal insufficiency.

To correct the initial hypovolemia and hyponatremia, patients with acute adrenal insufficiency must be treated with volume replacement as appropriate. Using hourly bedside monitoring, blood sugar levels below 60 mg/dl should be avoided and treated with intravenous dextrose as indicated. Subsequent fluid therapy should be continued as directed by the patient's clinical status and ongoing fluid losses. Evaluation of the patient's continuing fluid needs must be performed at 4 hour intervals to determine if the scheduled replacement is adequate to compensate for persistent volume and salt requirements.

Replacement intravenous fluids should be potassium free for the first 24 hours unless the serum potassium level drops below 3.5 mEq/L. When signs of hyperkalemic electrocardiographic toxicity exist, the patient must be treated aggressively to avoid clinical toxicity. If the patient develops a non-perfusing dysrhythmia due to extreme hyperkalemia (this frequently may resemble ventricular tachycardia on

the EKG), IV calcium should be given immediately. Although parenteral calcium is potentially effective in converting the dysrhythmia to a perfusing sinus rhythm, hyperkalemic dysrhythmias will recur unless the serum potassium level can be reduced. A fast, simple way to reduce the serum potassium although only temporarily, is by administering sodium bicarbonate 1 mEq/kg IV. Sodium bicarbonate is readily available and requires no special preparation to administer. Sodium bicarbonate works by raising the serum pH and shifting potassium intracellularly, thus lowering the serum potassium. Other rapid measures for treating severe hyperkalemia by similarly shifting potassium intracellularly include: 1) albuterol aerosol and 2) insulin (0.1 unit per kg) IV. It is important to administer insulin with a concurrent dextrose containing IV solution to avoid hypoglycemia. These latter potassium-lowering methods are only temporary since they merely shift potassium intracellularly. Excess potassium must be removed from the body by administering sodium polystyrene sulfonate (Kayexalate) resin. Kayexalate exchanges sodium for potassium thereby increasing the patient's serum sodium while removing potassium. Kayexalate may be given PO or as a retention enema. Furosemide IV may also be used to remove excess potassium through its effect in increasing renal sodium and potassium excretion.

Acute episodes of adrenal insufficiency usually resolve by the second day of appropriate therapy. Intravenous fluids containing a sodium chloride solution with dextrose should be continued until the institution and tolerance of oral feedings allows for adequate sodium intake. Patients with salt-losing adrenal insufficiency, especially infants, may require prolonged oral sodium replacement, which may be given in conjunction with feedings. Likewise, in the older child with adrenal insufficiency secondary to an acute episode of Addison's Disease, supplementary sodium may be similarly needed in some patients and may be added to their meals as tolerated.

In the chronic long-term management of CAH, insufficient glucocorticoids result in excess ACTH stimulation of adrenal androgen production, which leads to virilization and premature puberty with eventual short stature. Alternatively, excess glucocorticoids result in clinical findings of hypercortisolism such as central weight gain, striae, hypertension, and growth suppression. Adrenal androgen levels, 17OHP and androstenedione, can be monitored to assess the adequacy of glucocorticoid replacement. Elevated levels indicate inadequate glucocorticoid treatment with incomplete suppression of excess ACTH release. Low adrenal androgen levels may indicate that glucocorticoid dosing is excessive especially if associated with age-inappropriate growth rates or other clinical evidence of an excess glucocorticoid effect. The adequacy of mineralocorticoid dosing may be monitored through serial determinations of plasma renin and electrolyte levels. Elevated renin levels indicate an insufficient mineralocorticoid replacement regimen even in the absence of associated hyponatremia or hyperkalemia. Suppressed plasma renin may alternatively suggest an excess mineralocorticoid effect especially in the presence of an elevated blood pressure.

Other adrenal conditions in pediatrics are less common. Cushing's syndrome is a symptom complex that reflects an excessive, peripheral adrenal glucocorticoid effect. This hypercortisolism may be iatrogenic or endogenous, the latter either primary from autonomous adrenal hyperactivity (ACTH-independent) or secondary to an excess ACTH stimulation (ACTH-dependent). When caused by excessive pituitary ACTH production, the condition is called Cushing's Disease. As suggested above, Cushing's syndrome may also be iatrogenic and result from exogenously administered corticosteroids used as therapy for various medical conditions. Symptoms of hypercortisolism from any cause are typically subtle, often nonspecific and slow to develop. Common findings consist of an increased subcutaneous fat deposition, especially in the temporal areas of the face ("moon facies"), the posterior neck ("buffalo hump") and the abdomen. These findings, however, are also seen with simple obesity. Other symptoms of hypercortisolism include facial plethora, easy bruising, cutaneous atrophy, striae, elevated blood pressure and, in children and adolescents, growth failure. This latter characteristic, especially when associated with increasing weight, is the most common presentation of Cushing's syndrome in pediatrics. Although not limited to Cushing's syndrome, decreasing height percentiles is a helpful diagnostic sign in differentiating hypercortisolism from exogenous obesity given that dietary overweight does not lead to poor growth and may in fact cause growth acceleration. In children less than 8 years, Cushing's syndrome is more commonly ACTH-independent and caused by either adrenal adenomas or carcinomas. Of interest, children with Cushing's syndrome from a virilizing adrenal carcinoma may actually present with growth acceleration from an associated, increased adrenal androgen production rather than with the growth failure commonly seen with hypercortisolism. Alternatively, in older children, ACTH-dependent Cushing's from pituitary corticotroph adenomas (Cushing's disease) accounts for about 50 percent of the cases.

The diagnosis of Cushing's syndrome is confirmed by findings of elevated, non-suppressible levels of glucocorticoids, determined either as serum cortisol concentrations or as 24-hour urinary excretion rates of 17OHCS or free cortisol. Differentiation of ACTH-dependent and independent types, as well as localization of the source of the hypercortisolism, may be achieved through a variety of suppression and stimulation studies. Their discussion, however, is beyond the scope of this book. Treatment of Cushing's syndrome is usually surgical, with subsequent adrenal hormone replacement, and is directed at correction of the primary cause. Medical therapy is often of last resort and only poorly effective.

Adrenal disorders localized to the adrenal medulla are even more rare, especially in pediatrics. Pheochromocytomas are catecholamine-producing tumors of neural crest origin. The vast majority are benign and localized to the adrenal gland although extra-adrenal pheochromocytomas are not uncommon in children. The presenting clinical symptoms are directly related to the excess catecholamines released by these tumors. Relevant among these are cold clammy skin, tachycardia, anxiety, agitation and potentially life-threatening hypertension from systemic vasoconstriction. Because release of catecholamines by these tumors is typically episodic, so may the patients' symptoms be also intermittent. The diagnosis may thus be difficult to establish and may require multiple investigations. The diagnosis however, may be confirmed by findings of significantly elevated blood and/or urine levels of catecholamines and their metabolites especially at the time of clinical symptoms. Pheochromocytomas may occur as unilateral or bilateral adrenal tumors (bilateral is more common in children) and either as an isolated or a familial phenomenon, the latter being often part of the Multiple Endocrine Neoplasia syndromes. Treatment is directed at surgical removal of the primary tumor with pre-operative, medical stabilization of the associated hypertension.

Neuroblastomas, ganglioneuromas and ganglioneuroblastomas are additional tumors of the adrenal medulla. Although these tumors may excrete catecholamines, characteristically dopamine and its metabolite, homovanillic acid (HVA), most are nonfunctional and detected through findings, often incidental, of an abdominal mass. Treatment is surgical with subsequent chemotherapy as indicated by the pathology findings.

Questions

1. Urinary excretion rates of 17-hydroxycorticosteroids (17-OHCS) reflect the blood levels of:
   a. Mineralocorticoids
   b. Glucocorticoids
   c. Sex steroids
   d. Adrenal androgens

2. The daily secretory rate for plasma cortisol is approximately:
   a. 5 mg / square meter / day
   b. 12 mg / square meter / day
   c. 25 mg / square meter / day
   d. 50 mg / square meter / day

3. Congenital adrenal hyperplasia due to 21-alpha-hydroxylase deficiency is inherited as a(n):
   a. Autosomal recessive trait.
   b. Autosomal dominant trait.
   c. X-linked recessive trait.
   d. Sporadic disorder from a spontaneous gene mutation.

4. Acquired adrenal insufficiency in school age children and adolescents may present with:
   a. Hypertension and a "Buffalo Hump".
   b. Hypernatremia and hypokalemia.
   c. Hypoglycemia and postural hypotension.
   d. Biochemical findings of suppressed ACTH levels.

5. Chronic, primary adrenal insufficiency (Addison's disease) in children is most commonly due to:
   a. Tuberculosis
   b. Adrenal hemorrhage
   c. Autoimmunity
   d. Tumor

6. True/False: If patients have received large doses (i.e., greater than physiologic replacement) of glucocorticoids for a short period of time (i.e., less than one month) or small doses (i.e. less than physiologic replacement) for any period of time, adrenal function will likely resume shortly after cessation of therapy.

7. Which of the following is a hypertensive form of congenital adrenal hyperplasia?
   a. Simple virilizing 21-hydroxylase deficiency
   b. Salt-losing 21-hydroxylase deficiency
   c. 11-hydroxylase deficiency
   d. 3-beta dehydrogenase deficiency

8. Which of the following laboratory tests are most appropriate for monitoring the effectiveness of steroid replacement therapy in acquired, primary adrenal insufficiency ?
   a. 17-OH progesterone, androstenedione and ACTH levels.
   b. fractionated catecholamines and homovanillic acid (HVA) levels.
   c. post-dexamethasone urinary free cortisol and 17OH corticosteroids levels.
   d. ACTH, plasma renin and serum electrolyte levels.

9. A 2 week old infant presents with projectile vomiting and dehydration. The infant's electrolytes are as follows: Na 126, K 6.5, Cl 92, Bicarb 15, glucose 60. These electrolyte results are most compatible with which of the following diagnosis ?
   a. pyloric stenosis with bicarbonate loss from repeated vomiting.
   b. congenital Cushing's syndrome from excess mineralocorticoid effect.
   c. pheochromocytoma from excess catecholamine effect.
   d. salt-wasting CAH from mineralocorticoid deficiency.

10. Cushing's syndrome is characterized by the presence of:
   a. hyponatremia and hyperkalemia.
   b. an elevated urinary free cortisol excretion.
   c. genital virilization from excess adrenal androgens.
   d. low serum cortisol and increased ACTH levels.

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Answers to questions

1.b, 2.b, 3.a, 4.c, 5.c, 6.True, 7.c, 8.d, 9.d, 10.b

Chapter XV.5. Antidiuretic Hormone

Daniel C. H. Kidani, MD

This is a 1 year old male who presents to the office with a chief complaint of increased urination and thirst. Over the past month, he has been wetting an increasing number of diapers, >15 per day which is associated with increased fluid consumption. He always has a bottle or training cup in his hand, and his parents feel that this is abnormal.

Exam: VS are normal. Weight is at the 75th percentile. He is alert and active, in no distress. He is slightly large for age. No abnormalities are detected on physical examination. No ketosis is detected and he exhibits no signs of dehydration.

Labs: UA is normal. Urine specific gravity is 1.005. No glycosuria is noted. CBC WBC 8.0, Hgb 16.5, Hct 48.7, Platelet count 324,000. Chemistry: Na 149, K 4.4, Cl 99, CO2 22, Glucose 102.

How would you work this patient up?

Antidiuretic hormone (ADH) is a short peptide also known as 8-arginine-vasopressin (AVP) (1). It is synthesized in the supraoptic and paraventricular nuclei of the anterior hypothalamus and is subsequently transported via neurons to the posterior pituitary gland where it is stored as granules and released into the systemic circulation through the cavernous sinus and superior vena cava (2).

The main biologic effect of ADH is to reduce the rate of urine flow by increasing the reabsorption of solute-free water from the filtrate in the distal tubules and collecting ducts of nephrons (1). This response is mediated by specific V2 receptors located on the basolateral surface of the principle cells of collecting ducts to induce water reabsorption. In their resting state, V2 receptors are inactive, and the distal tubules and collecting ducts are impermeable to water (2). Once V2 receptors are activated by ADH, a G-protein-coupled adenylcyclase is activated which converts ATP to cAMP which then activates a protein kinase. This protein kinase induces vesicles containing water channels, made up of the protein aquaporin-2 (2), to migrate to the apical cell membrane resulting in increased permeability to free water. Water is reabsorbed into the cell and passes through the freely permeable basolateral membrane into the peritubular capillaries (1). As a result of the increased permeability, most of the water in the diluted filtrate that reaches the distal nephron back diffuses down the osmotic gradient created by the hypertonic milieu of the surrounding renal medulla. This back diffusion of water in the absence of solute increases urine concentration and reduces urine flow by an amount proportional to the level of ADH. ADH also increases NaCl reabsorption in the thick ascending loop of Henle. These effects of ADH result in tubular conservation of water, increased urine osmolality, decreased plasma osmolality, and negative free water clearance without significant alteration in solute excretion. However, ADH is rapidly reversible once plasma levels decline as its half-life is between 5 and 15 minutes (1).

ADH also acts on V1 receptors located in smooth muscle and can cause contraction of the GI tract as well as all parts of the vascular bed (vasoconstriction), especially the small arterioles and venules (hence, its other name, vasopressin) (1). This effect on the contractile elements are neither antagonized by adrenergic blocking agents nor prevented by vascular denervation.

Granules of ADH are released when hypothalamic osmoreceptors sense an increase in serum osmolality, even as little as 1% above normal. The threshold range for ADH secretion is 280-290 mOsm/liter. Once the threshold range is exceeded, there is a steep rise in the release of ADH, resulting in a decrease in serum osmolality back toward normal while increasing the osmolality of urine (1).

Regulation of ADH secretion is mediated by osmoreceptors that are thought to be located in the anteromedial hypothalamus near the neurohypophyseal cell bodies in the supraoptic nucleus. These osmoreceptors are normally sensitive to small changes in effective osmotic pressure such that a decrease in plasma osmolality as small as 1% to 2% rapidly suppresses ADH secretion to levels that permit a maximum water diuresis. Above this set-point, plasma ADH rises steeply in direct proportion to plasma osmolality and reaches a level sufficient to produce a maximum antidiuresis before plasma osmolality or serum sodium exceed the normal range; typically 275 to 295 mOsm/lit in a healthy individual. However, the sensitivity and the slope of the ADH response varies widely between individuals, and is thought to be genetically determined. This set-point is reduced during pregnancy and the luteal phase of the menstrual cycle (hence, more fluid retention), but increased in the elderly (hence, less fluid retention) (2).

Non-osmotic variables can also influence ADH secretion. Reductions in blood volume or arterial pressure of more than 10% to 20% stimulate release of ADH. This is thought to be due to lowering the set-point of the osmoregulatory system, mediated by neural pathways that originate in stretch receptors in the walls of the left atrium and large arteries. These pathways project via the vagal and glossopharyngeal nerves to the brain stem and eventually to the hypothalamus where they interact via an as of yet unknown way with input from osmoreceptors. Under normal conditions, this pathway seems to have little or no influence on ADH secretion; however, in conditions such as severe congestive heart failure, adrenal insufficiency, and other diseases associated with large reductions in blood pressure or blood volume, this pathway may have a profound effect (2).

ADH released via this pathway is released in concentrations 10-1000 times greater than normal. At these high concentrations, ADH acts as a vasoconstrictor, especially at the outer renal cortex. This is mediated by activation of V1 receptors which exist on vascular smooth muscle, glomerular mesangial cells, and the vasa recta and is mediated through the phosphatidyl-inositol pathway (1). Thus, hypovolemia-induced secretion of ADH is a more potent stimulant for ADH release than is serum osmolality and contributes to the SIADH (fluid retention, hypoosmolality, and hyponatremia) seen in postoperative patients (1).

Nausea is another potent stimulus for ADH release under pathologic conditions (e.g., vasovagal reactions, emotional stress with a vasovagal reaction, hyperemesis gravidum, diabetic ketoacidosis, chemotherapy, motion sickness). Even if transient and unassociated with emesis or changes in blood pressure, nausea can result in rapid 20- to 500-fold increases in plasma ADH levels (2).

The function of ADH is to decrease water loss; however, its ability to do so is limited because it cannot reduce the rate of urine output below the amount required to excrete a given solute load and cannot eliminate insensible losses such as the evaporation of water from the skin and lungs. Thus, another mechanism to replace this water loss must exist. This vital function is carried out by the thirst mechanism (2).

Thirst is regulated primarily by hypothalamic osmoreceptors; however, these osmoreceptors are less sensitive than those for ADH release. The osmotic threshold at which thirst begins is about 5 to 10 mOsm/kg higher than the threshold for ADH release (2).

Diabetes insipidus is an uncommon syndrome characterized clinically by increased fluid intake and the excretion of abnormally large volumes of urine of low specific gravity. It is caused by a deficiency of or a resistance to ADH (3). The most common cause is a primary deficiency of ADH secretion, usually referred to as pituitary, neurogenic, neurohypophyseal, cranial, or central diabetes insipidus. It is almost always the result of irreversible destruction of more than 80% of ADH-producing magnocellular neurons secondary to acquired, congenital, or genetic diseases (2).

Congenital causes include septo-optic dysplasia, cleft lip and palate, other midline craniofacial defects, holoprosencephalic syndromes, and agenesis/hypogenesis of the pituitary. Primary central diabetes insipidus can also be caused by head trauma, primary tumors (craniopharyngiomas, adenomas, meningiomas, dysgerminoma), and metastatic (breast, lung) tumors, lymphomas, granulocytic leukemias, neurosarcoid, histiocytosis, xanthoma disseminatum, chronic meningitis, viral encephalitis, toxoplasmosis, autoimmune conditions (lymphocytic infundibuloneurohypophysitis, scleroderma, Wegener's granulomatosis, SLE), Sheehan's syndrome, carotid aneurysms, hypoxic encephalopathy, snake venom, as well as idiopathic causes.

The most common genetic form of central diabetes insipidus is transmitted in a completely penetrant autosomal dominant fashion and involves the AVP-NPII gene on chromosome 20. The AVP (ADH) deficiency is not present at birth but develops several months to years later and may gradually progress from partial to severe (>95%). It is hypothesized that the mutant AVP-NPII gene produces a defective AVP prohormone which cannot be secreted, and thus accumulates within neurons and leads to neuronal death. A much rarer form of congential central diabetes insipidus is transmitted in an autosomal recessive mode which also involves the AVP-NPII gene, but unlike its autosomal dominant counterpart, leads to the production of a mutant AVP with little or no antidiuretic effect (2).

A primary deficiency of plasma ADH can also occur during pregnancy and is known as gestational diabetes insipidus. In this case, the deficiency is a result of degradation of ADH by a vasopressinase produced in the placenta. Polyuria, thirst, and polydipsia typically occur during the third trimester which usually remits 3 to 6 weeks after delivery (3).

Decreased ADH is not always the cause of diabetes insipidus. Rather, a deficiency in the responsiveness of ADH at its site of action may also cause polyuria. This form of diabetes insipidus is termed nephrogenic. These patients have normal secretion of AVP and are unresponsive to exogenous vasopressin. The abnormality lies in a defective expression of vasopressin V2 receptors or vasopressin-sensitive water channels (3).

The most common form of genetic nephrogenic diabetes insipidus is transmitted in an X-linked recessive mode. It is congenital and often results in repeat episodes of hypernatremic dehydration during the first 2 years of life. It is refractory to the antidiuretic effect of normal to modestly increased levels of plasma ADH, but it may respond to high pharmacologic doses of deamino-D-arginine vasopressin (DDAVP, a synthetic vasopressin) (2).

Less common forms of congenital nephrogenic diabetes insipidus are transmitted in autosomal dominant and autosomal recessive modes. These conditions are caused by mutations in the coding region of one or both aquaporin-2 genes and usually result in severe or complete resistance to ADH (2).

Acquired forms of nephrogenic diabetes insipidus are usually less severe than genetic forms. It is seen in pyelonephritis, renal amyloidosis, myeloma, potassium depletion, Sjogren's syndrome, sickle cell anemia, hypercalcemia, sarcoma, and neurosarcoid of the kidney. Acute tubular necrosis may also be associated with a transient nephrogenic diabetes insipidus. Glucocorticoids, diuretics, demeclocycline, lithium, foscarnet, and methicillin may all cause nephrogenic diabetes insipidus (2).

The pathophysiology that underlies central, gestational, and nephrogenic diabetes insipidus are similar. In all three, the kidneys are unable to concentrate urine resulting in a diuresis that results in a slight (1% to 2%) decrease in body water and an increase in basal plasma osmolality and sodium. Increased serum osmolality stimulates thirst and a compensatory increase in water intake, preventing further dehydration. Thus, unless the thirst mechanism is damaged or the patient is unable to increase fluid intake, water and osmolar homeostasis are maintained.

In all types of chronic diabetes insipidus, the maximum urinary concentrating capacity is reduced and is proportional to the severity of the diabetes insipidus. It is thought that this may be the result of washout of the medullary concentration gradient or inhibition of aquaporin-2 synthesis. However, it usually corrects within 24 to 72 hours if polyuria is eliminated (2).

The hallmarks of diabetes insipidus are polyuria (2-20 liters per day) and increased fluid intake (3). Polyuria results in symptoms of urinary frequency, nocturia, incontinence, or enuresis. Fatigue may be an associated complaint resulting from frequent disruption of sleep. Polyuria is always accompanied by a proportionate polydipsia that is usually, but not always, attributable to increased thirst (2).

Physical exam findings including vital signs and routine laboratory studies are usually unremarkable. However, dehydration and hypernatremia may be present especially after hypothalamic damage secondary to shock or anoxia (3). Neurologic symptoms may be present depending on the etiology of the DI, such as hyperphagia, visual field defects, anosmia, weight loss, etc. (2).

Evaluation for DI should include a 24-hour urine collection for volume, glucose, and creatinine as well as serum studies for glucose, urea nitrogen, calcium, uric acid, potassium, and sodium (3).

There is no single diagnostic test to make the diagnosis of diabetes insipidus. The diagnosis is made mainly on clinical grounds with some laboratory supportive evidence. However, hyperuricemia implicates central diabetes insipidus as decreased V1 stimulation decreases urate clearance. If diabetes insipidus is suspected, a supervised vasopressin challenge test should be administered. Desmopressin acetate (DDAVP, a vasopressin analogue) which has a long duration of action and an antidiuretic/pressor factor of approximately 3000 when compared to AVP (4), is given in an initial dose of subcutaneously, or intravenously, with measurements of urine osmolality obtained 12 hours prior and 12 hours after administration. If basal plasma ADH is low, or if the osmolality of urine collected 1 or 2 hours after subcutaneous injection of DDAVP is more than 50% greater than the pretreatment value, the patient has central diabetes insipidus. The dosage of desmopressin is doubled if the response is marginal. Patients with central diabetes insipidus notice a marked decrease in polyuria and polydipsia (2). In contrast, if basal plasma ADH is elevated, or if the administration of DDAVP results in

little or no increase in urine concentration, the patient has severe nephrogenic diabetes insipidus. A two day trial of DDAVP with ad lib fluid intake can also help to distinguish between central and nephrogenic diabetes insipidus (2).

Magnetic resonance imaging of the brain with and without gadolinium contrast may also be useful in determining the type and etiology of the diabetes insipidus. It cannot differentiate between central and nephrogenic diabetes insipidus, but it may be able to differentiate diabetes insipidus from primary polydipsia (2).

Central diabetes insipidus must be distinguished from other causes of polyuria. Therefore, Cushing's syndrome as well as glucocorticoid therapy, diabetes mellitus, drugs (carbamazepine, lithium), psychogenic polydipsia, central nervous system sarcoidosis, as well as intravenous fluid administration must be considered (3). Psychogenic water drinking can be extremely difficult to distinguish from DI. Withholding water from such patients will often result in anxiety, but withholding water from patients with DI, is dangerous. Thus, until the diagnosis can be confirmed, an evaluation for DI in uncertain cases, must often be done as an inpatient to establish the diagnosis. In theory, psychogenic water drinkers should not have hypernatremia.

The signs and symptoms of diabetes insipidus can be eliminated completely by replacing the AVP deficiency with DDAVP. DDAVP is a synthetic analogue of vasopressin but is more resistant to degradation, has less of a pressor effect, and can be given by mouth, nasal spray, or injection (4). The dose required to normalize the 24-hour urine volume and concentration varies from patient to patient and must be determined empirically. The typical requirements in adults are 50 to 200 mcg by mouth two to three times a day, 5 to 20 mcg by nasal spray two to three times a day, or 1 to 2 mcg by subcutaneous injection once or twice a day. Patients rarely develop water intoxication due to homeostatic mechanisms; however, patients on DDAVP should be advised to drink only when truly thirsty (2). Adverse reactions to DDAVP include nasal irritation, agitation, and erythromelalgia (throbbing and burning pain in the skin often precipitated by exertion or heat). Hyponatremia is rare if the patient is placed on the minimum effective dose and thirst is allowed to occur periodically (3).

The signs and symptoms of nephrogenic diabetes insipidus are completely unaffected by standard doses of DDAVP unless the process is partial in which case tenfold higher doses are effective. The expense and inconvenience of this treatment, however, make this regimen impractical. If hypokalemia, hypercalcemia, or the use of lithium is present, the correction of the underlying problem may correct the diabetes insipidus (lithium can cause nephrogenic DI); however, in many cases this is difficult to accomplish. Treatment usually consists of a low sodium diet coupled with an empirically determined combination of chlorothiazide, hydrochlorothiazide, amiloride, or indomethacin. Patient's typically experience a 50% to 70% decrease in urine volume (2).

The syndrome of inappropriate ADH secretion (SIADH) is a disorder characterized elevated levels of ADH which hinders the ability of the kidneys to dilute urine resulting in water intoxication with hypotonicity and hyponatremia (4). In pediatrics, SIADH is most commonly encountered in patients with bacterial meningitis. A urine sodium should be immediately obtained once hyponatremia is identified. A low urine sodium (coupled with hyponatremia) is abnormal and indicative of SIADH.

Patients may develop symptoms of hyponatremia ranging from mild headaches, anorexia, and confusion to nausea, vomiting, coma, convulsions, and death (2). However, hyponatremia may be asymptomatic if it has developed gradually. Symptomatic hyponatremia has a mortality of 10 to 15%, and the mortality rate is higher when the serum sodium level is below 110 mEq/L (4).

Patients may experience weight gain because of water retention; however, edema is not present because the retained water is distributed among both extracellular and intracellular compartments. Signs of congestive heart failure, cirrhosis, nephrosis, or hypovolemia are also absent (2).

Acute water retention causes neurologic symptoms by rapidly increasing the intracellular volumes of brain cells and thus inducing cerebral edema. It is probable that chronic hyponatremia is less symptomatic because there is time for activation of compensatory volume-regulatory mechanisms in the central nervous system. Brain cells compensate for volume gain by activating ion transport processes that pump out intracellular KCl and NaCl. This compensation has therapeutic importance, because rapid correction of hyponatremia by infusion of hypertonic saline produces a transient hypertonic encephalopathy as water is drawn out of the already contracted intracellular space. This can cause permanent neurologic damage, for example central pontine myelinolysis and death (4).

In most patients with SIADH, the defect in urinary dilution is caused by ectopic production, exogenous administration, or osmotically inappropriate neurohypophyseal secretion of ADH. Associated conditions (not necessarily etiologies) include brain malformations, midline defects, ectopic secretion from neoplasms (e.g., small cell lung cancer), other cancer conditions, drugs, severe neurological conditions (meningitis, severe head trauma, encephalitis, coma, etc.), severe pneumonia, respiratory failure (with mechanical ventilation), etc. (4).

ADH is synthesized as a prohormone of 166 amino acids that is processed to produce three peptides: the mature octapeptide hormone, a midregion 10,000-molecular-weight peptide with vasopressin-binding activity called neurophysin II, and a C-terminal glycopeptide. Both the vasopressin (ADH) and the neurophysin are packaged within the neurosecretory granule (4).

Neuroendocrine tumor cells produce ADH in a similar fashion, secreting both vasopressin and neurophysin II. However, vasopressin's sister peptide oxytocin together with its binding protein, neurophysin I, are also commonly secreted. The proximity of the genes for vasopressin and oxytoxin, less than 12kb within the human genome, is thought to explain this phenomenon as a single transcription factor could activate both promoters (4).

Water retention leads to expansion of both the extra and intracellular compartments. The expansion of extracellular fluid volume (likely secondary to suppression of aldosterone and increased atrial natriuretic peptide release) leads to natriuresis (sodium excretion) and a reduction in fluid volume in patients with an adequate sodium intake.

Plasma AVP and AVP analogues do not significantly lower serum sodium unless total water intake (dietary plus insensible) exceeds total output (urinary plus insensible). When such imbalance occurs, the excess water cannot be excreted as quickly as is normal because urinary concentration cannot decrease sufficiently to permit a fully compensatory water diuresis. Consequently, water is retained in the extracellular and intracellular compartments; the concentration of sodium and other solutes in body fluids is diluted; plasma urea, uric acid, rennin and aldosterone activities are reduced; and urinary sodium excretion increases as an appropriate response to the expansion of plasma and extracellular volume, via ANP (4). The natriuresis aggravates the dilutional hyponatremia but partially offsets the extracellular volume expansion, preventing edema or other signs of hypervolemia. The rate at which these abnormalities develop varies widely depending on the magnitude of the imbalance between the total rate of water intake and excretion by renal and extrarenal routes. If the defect in urinary dilution is minor or if insensible loss of water is abnormally high, even markedly increased rates of water intake may be insufficient to induce hyponatremia. On the other hand, if urinary concentration is fixed at a high level and insensible loss is low, even an apparently normal basal rate of fluid intake may be sufficient to produce the syndrome (2).

SIADH is generally diagnosed by finding a low serum osmolality in conjunction with a relatively high urine osmolarity. This is abnormal since the urine should be very dilute if the plasma is hypo-osmolar. Checking the serum and urine sodium levels are often sufficient since hyponatremia in conjunction with an elevated urine sodium is similarly abnormal, although this can also be caused by diuretics, mineralocorticoid deficiency (Addisonian crisis) and salt losing nephropathy.

The clinical presentation of SIADH can vary appreciably owing to differences in the type of osmoregulatory defect present. The most striking and potentially confusing variant is that caused by downward resetting of the osmostat. In this type of defect, plasma AVP and urine concentration continue to be osmoregulated and can still be maximally suppressed if fluid intake is great enough to lower plasma osmolality/sodium to the new threshold or set point. Consequently, patients with this variant of SIADH may present with hyponatremia and maximum urinary dilution, leading to the false conclusion that polydipsia alone was responsible for the fluid-electrolyte imbalance. If the measurements of urine osmolality are repeated during therapeutic fluid restriction, the true cause becomes apparent because urinary concentration begins long before serum sodium rises to normal. Close monitoring of urine output and serum sodium is important for effective clinical management in all variants of SIADH because the abnormal AVP secretion of any type can suddenly remit, allowing a brisk water diuresis that raises the serum sodium more rapidly than may be safe. Such remissions are relatively common in SIADH because it is usually an acute self-limited disorder that lasts only a few days or weeks (2).

The SIADH must be differentiated from hypervolemic, hypovolemic, and other forms of euvolemic hyponatremia. These distinctions can usually be made on the basis of the clinical history, physical examination, and routine laboratory tests. Hypervolemic hyponatremia occurs in patients with severe congestive failure, cirrhosis, or nephrosis, and is always associated with edema. The osmotic suppression of plasma AVP and urinary dilution are also impaired, but, in this case, the defect is caused by a reduction in effective blood volume, which stimulates AVP release via the baroregulatory system. Because of this effective hypovolemia, plasma urea, uric acid, renin activity, and aldosterone are also usually elevated, and the urinary excretion of salt and water is decreased.

Hypovolemic hyponatremia occurs in conditions such as diuretic abuse, mineralocorticoid deficiency, or gastroenteritis, which result in excessive loss of sodium and water. The resultant depletion of intravascular and interstitial fluid results in physical signs of hypovolemia, such as tachycardia and postural hypotension. It also increases plasma AVP and urine concentration and decreases renal perfusion. Consequently, plasma urea, uric acid, renin activity, and aldosterone are elevated, whereas urinary excretion of salt and water are reduced (unless a diuretic or sodium-losing nephropathy is responsible).

In addition to SIADH, euvolemic hyponatremia can result from isolated cortisol deficiency or emesis. The pathophysiology and clinical characteristics of the latter two forms of euvolemic hyponatremia are identical to SIADH, with the exception that they are associated with hypocortisolemia or a history of nausea and vomiting and can be corrected completely by treatment with cortisol or antiemetics (2).

In some patients, SIADH can be cured by eliminating the tumor, drug, or disease responsible for the syndrome. In others, it is an acute self-limited disorder that remits spontaneously within 2 to 3 weeks. The most common therapy used to treat SIADH is fluid restriction. This reduces free water retention and allows the hyponatremia to resolve gradually. If the hyponatremia is severe, or accompanied by symptoms such as nausea, vomiting, coma, or seizures, it may be desirable to correct part of it more rapidly by combining fluid restriction with a slow intravenous infusion of hypertonic (3%) saline. Hypertonic saline infusion is dangerous, requiring close monitoring and frequent stat sodium measurements (a turnaround time of 1 hour is not fast enough since the sodium may have risen to excessive levels before then). When infused at a rate of approximately 0.05 mL/kg/min, 3% saline raises serum sodium by about 2 mEq/L per hour. With this therapy and all other methods of treatment, urine output and fluid intake should be monitored closely because SIADH can remit spontaneously at any time, and, when it does, the resultant water diuresis may raise serum sodium too fast or too far if water intake is not allowed to increase. The objective should be to raise serum sodium no faster than 24 mEq/L in 24 hours and to a final level no greater than 135 mEq/L. Although this issue is not yet settled, raising the serum sodium faster or farther may cause acute osmotic demyelinization, a serious complication characterized by severe neurologic abnormalities, including quadriparesis, mutism, pseudobulbar palsy, seizures, behavioral disturbances, and movement disorders (2).

Chronic SIADH usually cannot be controlled by fluid restriction alone because thirst is also increased inappropriately; however, the hyponatremia may be corrected or prevented by treatment with demeclocycline (induces nephrogenic diabetes insipidus) or fludrocortisone (mineralocorticoid with aldosterone-like activity). When given at doses ranging from 150 to 300 mg two to four times a day, demeclocycline increases urinary free water excretion by interfering with the antidiuretic action of AVP. This effect may not occur for several weeks and is usually reversible when treatment is stopped. Demeclocycline may also cause photosensitivity, azotemia, or other signs of nephrotoxicity, but these side effects are usually also reversible. Treatment with fludrocortisone in doses of 0.1 to 0.3 mg twice a day can also be effective, presumably because it promotes sodium retention; however, it may also act in part by inhibiting thirst and fluid intake. The abnormalities in AVP secretion and AVP action are not affected by fludrocortisone. The principal side effects are hypokalemia and hypertension, which may necessitate potassium supplementation or reduction of the dose. AVP antagonists may also prove to be effective treatment for chronic SIADH in the future (2).

Questions

1. What is actions does ADH have?
2. What clinical manifestations might one see in a case of diabetes insipidus?
3. How might one distinguish nephrogenic from central diabetes insipidus?
4. Are levels of ADH under regulatory control in SIADH?
5. What is the most common neoplastic cause of SIADH?
6. If hyponatremia is found, what is the most useful next test to determine the etiology of the hyponatremia.
7. True/False: 3% sodium chloride solution (hypertonic saline) can be used safely to raise the serum sodium level in SIADH.

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Answers to questions

1. The main biologic actions of ADH are to reduce the rate of urine flow by increasing the reabsorption of solute-free water from the filtrate in the distal tubules and collecting ducts of nephrons. This occurs via V2 receptors. When ADH acts on V1 receptors it causes vasoconstriction and contraction of smooth muscle elements.
2. Besides polyuria and polydipsia, physical exam and lab studies are typically within normal limits. However, in severe cases, signs and symptoms of hypernatremia and dehydration may be present.
3. Vasopressin challenge test: polyuria and polydipsia are corrected in central diabetes insipidus, but not corrected with standard doses in nephrogenic diabetes insipidus.
4. Yes and No. There are 4 types, only one is regulated by osmolality; however, the osmostat is reset to a lower osmolality.
5. Small cell lung cancer
6. The urine sodium is the test that should be done next. If the urine sodium is low, then the hyponatremia is due to total body sodium depletion. If the urine sodium is high, then the hyponatremia is due to SIADH, Addisonian crisis, diuretics, or salt losing nephropathy.
7. False. Hypertonic saline infusion is dangerous.

Chapter XV.6. Calcium Disorders
David F. Crudo MD

This is a 16 month old female, who presents to the ED with an acute onset of her hands and feet "drawing up". Her parents report that she cries when touched in her hands and feet and has refused to walk. She had a low-grade fever, vomiting, diarrhea, and decreased urine output attributed to a viral gastroenteritis beginning four days ago. Past medical history reveals that she had been a healthy term infant with no previous hospitalizations or significant illnesses.

Exam: VS T 37.7, P 140, R 20, BP 90/64, length 74.5 cm (10%ile), wt 9.2 kg (10%ile). She is fussy but awake and alert. HEENT, neck, heart, lungs and abdomen exams are normal. Both her hands are flexed at the wrists with hyperextended fingers at the proximal and distal interphalangeal joints and flexion at the metacarpophalangeal joints. Both thumbs are flexed upon the palm. Her feet are plantar flexed. Neurologic exam reveals symmetric hyperreflexia, decreased muscle strength and tone.

Laboratory: Na 135, K 3.8, Cl 102, bicarbonate 24, BUN 5 mg/dL, creatinine 0.3 mg/dL, glucose 82 mg/dL, calcium 5.6 mg/dL (normal 8.5 to 10.5), phosphorus 2.2 mg/dL (normal 3.5 to 6), alkaline phosphatase 1020 U/L (normal 125 to 450), ionized calcium 0.50 mmol/L (normal 1.00 to 1.30). CXR shows enlargement of the costochondral junctions. The normal enlarged thymic shadow of infants and toddlers is present. Radiographs of hands/wrists demonstrate cuffing, fraying, and widening of the epiphysis and metaphysis.

A diagnosis of vitamin D deficiency rickets with acute hypocalcemic tetany is made and she is treated with 1 mL/kg of 10% Ca gluconate solution IV over 1 hour. A dietary history reveals that she had been breast-fed since birth that has continued at least twice a day at present. Table foods were introduced at 10 months of age, but she is described as a picky eater and does not drink whole milk. She does not take any vitamin supplements. A review of her growth curve shows her decreasing from the 50%ile for length and weight at birth to the 10%ile for both parameters now. The diagnosis is confirmed with serum 25-OH vitamin D level of <5 ng/mL (normal 10 to 55), with an appropriately increased PTH level of 270 pg/mL (normal 10 to 55). 1,25-dihydroxy vitamin D level is 40 pg/mL (normal 15 to 90) (The plasma concentration of 25-OH D is the most sensitive index of vitamin D nutritional status. Most untreated vitamin D deficient patients have normal or elevated levels of 1,25-dihydroxy vitamin D due to secondary hyperparathyroidism which increases activity of renal 1 alpha-hydroxylase, which converts 25-OH D to 1,25-diOH D).

She is admitted to the hospital and treated with oral supplementation of 250 mg calcium carbonate every six hours and 4,000 IU of vitamin D (ergocalciferol) per day. She has no further episodes of tetany and is discharged 2 days later continuing on calcium and vitamin supplementation. Clinical and radiographic improvement is noted over the next several months, and the vitamin D dose is reduced to the recommended daily allowance of 400 IU.

Calcium (1,3) is an essential component of the mineral portion of bone and as its divalent cation (Ca++) is necessary for the function of every cell. Maintenance of calcium homeostasis is a dynamic process involving calcium absorption and excretion in the intestine, filtration and reabsorption in the kidneys, and storage and mobilization in the skeleton. Nearly all of the total body calcium (98%) is present in very slowly exchangeable skeletal hydroxyapatite crystal. It is the rapidly exchangeable calcium in recently deposited bone (1% of body calcium) and in the extracellular, intracellular, and vascular spaces (1%), that plays critical roles in intracellular communication, interneuronal transmission, muscle contraction, clotting, cellular proliferation, synthesis of secretion of endocrine and exocrine factors, and as an enzyme cofactor. Total serum calcium is divided into three fractions: 40% is bound to albumin and globulin, 10% is complexed to anions, while 50% exists in the free ionized state that is necessary for most metabolic functions.

The serum concentration of calcium is maintained at normal levels by an integrated system involving the Ca++ sensing receptor (CaSR), parathyroid hormone (PTH), vitamin D, and calcitonin. The CaSR is a membrane protein that binds Ca++ and determines the set-point for PTH secretion. PTH is an 84 amino acid peptide that increases calcium concentration by stimulating reabsorption of calcium in the kidney, enhancing the rate of calcium resorption from bone and increasing the rate of absorption of calcium from the intestine through increased renal formation of 1-25-dihydroxy vitamin D (1,25-diOH-D). Vitamin D3 (cholecalciferol) is synthesized in the skin from 7-dehydrocholesterol by exposure to UV light and heat. Vitamin D3 is hydroxylated in the liver to 25-OH-D (calcidiol), then further hydroxylated in the kidney to the biologically active 1,25-diOH-D (calcitriol). 1,25-diOH-D stimulates the absorption or reabsorption of calcium in the intestines, bone, and kidney. Calcitonin is a 32 amino acid peptide secreted by the parafollicular (C) cells of the thyroid gland, secreted in response to a rise in the serum calcium concentration. Its major biological effect is to decrease the calcium resorption in bone by inhibiting osteoclast activity.

Etiology of Hypocalcemia in Children and Adolescents (2,3,4)

1. Hypoparathyroidism
   - Congenital
     - Transient neonatal
     - Familial
     - DiGeorge syndrome
   - Acquired
     - Autoimmune
     - Post-surgical
     - Infiltrative
   - Resistance to PTH
     - Pseudohypoparathyroidism
     - Pseudopseudohypoparathyroidism
2. Vitamin D deficiency
3. Other
   - Ca deficiency
   - Hypomagnesemia
   - Hyperphosphatemia
     - Includes chronic renal failure (renal osteodystrophy)
   - Hypoproteinemia
   - Drugs (furosemide, calcitonin, antineoplastic agents)
   - "Hungry bones"
   - Critical illness

The child with hypocalcemia may be asymptomatic and identified through chemistries obtained for another reason or present with intermittent muscular cramping, paresthesias, tetany, carpopedal spasms, laryngospasms, or seizures. Review of symptoms and past medical history may reveal intermittent symptoms associated with hypocalcemia. Commonly, the physical exam is unremarkable other than that of increased neuromuscular irritability: hyperreflexia, Chvostek sign (twitching of the circumoral muscles when tapping lightly over the facial nerve) or Trousseau sign (carpopedal spasm when maintaining a blood pressure cuff 20 mmHg above the systolic blood pressure for 3 minutes), and occasionally cataracts or abnormal dentition. The physical exam may disclose the characteristic phenotype of Albright hereditary osteodystrophy (short stature, round facies, shortened metacarpals, subcutaneous calcification; pseudohypoparathyroidism type Ia), the DiGeorge syndrome (typical facies, cardiac abnormalities), or rachitic changes (bowed legs or "knock knees", widened metaphyses of the long bones, prominent costochondral junctions, frontal bossing) in the case vitamin D deficiency.

DiGeorge syndrome is usually classified as an immune deficiency, but it usually presents initially with congenital heart disease or with hypocalcemic seizures or tetany. During embryogenesis, the thymus and parathyroid glands originate from the same branchial pouch, which explains why the two abnormalities occur together. Congenital heart disease may be detected during the newborn period. Subsequently, the child will present with hypocalcemic tetany or seizures during the first few months of life, before any opportunistic infection is likely to occur. A chest X-ray will show a cardiac silhouette without the usual thymic shadow. Thymic absence with hypocalcemia, is highly indicative of DiGeorge syndrome.

The laboratory evaluation of a hypocalcemic child requires measuring serum total and ionized calcium, PTH, magnesium, phosphate, creatinine, alkaline phosphatase, and urinary calcium. If there are concerns of a metabolic bone disease, serum levels of 25-OH-D and 1,25-diOH-D should also be obtained.

Calcium and magnesium tend to be antagonistic, so hypocalcemia will occur in association with a high magnesium load, which most commonly occurs in premature neonates of mothers treated with magnesium tocolytics. Severe hypomagnesemia will also result in hypocalcemia since magnesium is a required co-factor for PTH release. Thus, both extremes of magnesium, will result in hypocalcemia.

A patient with hypocalcemia, hypocalciuria, hyperphosphatemia, and low serum PTH levels has hypoparathyroidism caused by a primary defect in PTH synthesis or secretion. An elevated PTH level indicates a compensatory increase in response to hypocalcemia or a resistance to PTH (pseudohypoparathyroidism).

Management of symptomatic acute hypocalcemia is intravenous 10% calcium gluconate (93 mg elemental Ca in 10 mL), 1-2 mL/kg over 10 minutes. Although calcium chloride can also be used, some texts discourage the use of calcium chloride because it can lead to metabolic acidosis. After acute symptoms have resolved, an intravenous infusion of calcium should be initiated at a rate to keep the serum calcium levels in the low normal range while an investigation of the etiology ensues. Therapy for patients with hypo- or pseudohypoparathyroidism is individualized using calcitriol (20-60 ng/kg/day) and supplemental oral calcium (30-75 mg elemental Ca/kg/day). Frequent measurements of serum calcium and creatinine and renal ultrasonography are done to monitor for hypercalcemia, hypercalciuria, and nephrocalcinosis.

Etiologies of Hypercalcemia in Children and Adolescents (2,3,4)

1. Hyperparathyroidism
   - Sporadic
   - Familial (isolated or MEN 1 and 2A)
   - Secondary/tertiary (renal failure)
2. Familial hypocalciuric hypercalcemia (FHH)
3. Hypervitaminosis D
   - Nutritional
   - Granulomatous disease (sarcoidosis, TB, histoplasmosis)
4. Immobilization
5. Neoplasia
   - Bony metastases
   - Production of PTH related protein (PTHrP)
   - Cytokine/osteoclast-activator production
6. Other
   - Hyperphosphatemia
   - Drugs (thiazides, lithium, vitamin A, alkali)
   - Hyperthyroidism
   - Hypoadrenalism
   - Pheochromocytoma

Clinical features are dependent on the underlying disorder and degree of hypercalcemia. Nonspecific symptoms include polydipsia, polyuria, anorexia, constipation, nausea, vomiting, abdominal pain, weakness, and altered consciousness. The patient may show signs of dehydration or altered mental status, otherwise the physical exam is usually normal. Commonly a shortened QT interval can be found on EKG and nephrocalcinosis and renal calculi demonstrated by ultrasonography.

The initial laboratory evaluation of a hypercalcemic child requires measuring serum total and ionized calcium, urinary calcium, PTH, phosphate, creatinine, 25-OH-D and 1,25-diOH-D levels. If the patient is hypocalciuric, the probable etiology is FHH (familial hypocalciuric hypercalcemia). This diagnosis can be confirmed by finding asymptomatic hypocalciuric hypercalcemia in one of the parents. In the absence of secondary hyperparathyroidism (chronic renal failure, ingestion of thiazides or lithium), consistently elevated PTH levels are indicative of primary hyperparathyroidism. Calcidiol levels are increased in patients with hypercalcemia caused by excessive intake of vitamin D. Calcitriol levels are increased in patients with granulomatous, chronic inflammatory, and lymphomatous diseases or those receiving that vitamin. PTHrP (PTH related peptide) levels are high in the children with humoral hypercalcemia of malignancy.

Appropriate management depends on the severity and cause of the high calcium levels. If the calcium level is <12 mg/dL and the patient asymptomatic, treatment may be delayed pending evaluation of the cause. Symptomatic patients and those with calcium levels >12 mg/dL should be treated because of the adverse effects of hypercalcemia on the cardiac, renal, gastrointestinal, and central nervous systems.

Treatments are: 1) intravenous fluid therapy (NS at twice maintenance) to restore volume, dilute serum Ca++ levels, and promote calciuresis; 2) calciuresis by IV furosemide (1 mg/kg) only after restoration of volume; and 3) inhibition of bone resorption by bisphosphonates or calcitonin. Dialysis may be indicated if the patient is resistant to conventional therapy.

Surgery is indicated for primary hyperparathyroidism. The secondary hyperparathyroidism of chronic renal failure is best treated by lowering the serum phosphate to the extent possible while maintaining the serum calcium level in the low-normal range with calcitriol (1,25-diOH-D).

Glucocorticoids are effective in lowering excess calcium levels due to vitamin D ingestion, granulomatous and inflammatory diseases, or malignancies, by inhibiting renal 25-OH-D-1-alpha-hydroxylase activity. A low calcium diet, copious fluids, avoidance of vitamin D, and early mobilization are indicated in the immobilized child to avoid hypercalcemia.

Etiologies of Rickets (2,5)

1. Abnormality of vitamin D intake or metabolism
   - Nutritional deprivation (low birth weight infant, malabsorption, drugs)
   - Metabolic factors
   - 25-hydroxylase deficiency (loss-of-function mutation, severe liver disease)
   - 25-OH-D-1-alpha-hydroxylase deficiency (loss-of-function mutation, chronic renal insufficiency)
   - Loss-of-function mutation of vitamin D receptor
2. Calcium deficiency
   - Nutritional
   - Hypercalciuria
3. Phosphorus deficiency
   - Nutritional (low birth weight infant, aluminum-containing antacids)
   - Hyperphosphaturia
     - X-linked familial hypophosphatemic rickets
     - X-linked recessive hypophosphatemic rickets
     - Autosomal recessive hypophosphatemic rickets with hypercalciuria
     - Autosomal dominant hypophosphatemic rickets
     - Oncogenic hypophosphatemic osteomalacia
     - Renal tubular acidosis
4. Hypophosphatasia

Rickets and osteomalacia are disorders that result from demineralization of bone matrix. Rickets occurs in the growing child and involves the growth plate and can lead to skeletal deformities. Osteomalacia refers to demineralization of mature bone and is associated

with an increased fracture risk. Rickets is primarily calcipenic (nutritional deficiency of calcium or vitamin D or abnormality in vitamin D action) or phosphopenic (abnormality in renal reabsorption of phosphate).

Clinical signs of rickets in ambulatory children include bowed legs or "knock knees", widening of the long bones metaphyses, prominence of costochondral junction (rachitic rosary), frontal bossing, and short stature. Symptoms may include hypotonia, weakness, anorexia, and delayed walking. Hypocalcemia, tetany, and seizures may be seen in a severely vitamin D deficient infant.

Radiographically, the long bones are the earliest and most common sites of change. There is decreased bone density, thinning of the cortex, and widening, cupping, and fraying of the distal ends of the shaft.

In children with vitamin D deficiency, the serum calcium levels are normal or low, phosphate low, alkaline phosphatase elevated, calcidiol low, and calcitriol variable (i.e., it is sometimes normal as in the case). Prevention is the best treatment for vitamin D deficiency, but once deficiency has been established, treatment consists of vitamin D replacement (1000-4000 IU/day orally for several weeks; 10,000-50,000 IU IM monthly for 3-6 months; or 600,000 IU IM once). Calcium supplementation (elemental Ca 40 mg/kg/d) should be given to avoid hypocalcemia resulting from remineralization ("hungry bone" syndrome).

There is an association of prolonged breast-feeding and vitamin D deficiency. Breast milk has only 15-30 IU/L vitamin D. In 1997, the American Academy of Pediatrics issued a statement recommending vitamin D supplementation "for those infants whose mothers are vitamin D deficient or those infants not exposed to adequate sunlight" (6). However in 2003, the AAP revised this statement recommending vitamin D supplementation for all infants and children (7).

Rickets caused by inadequate dietary calcium has been observed in infants and children receiving a diet containing less than 200 mg elemental calcium per day. Ensuring adequate calcium intake established for growing children (1000-1300 mg/d) is preventative and therapeutic. Phosphate is abundantly present in most foods, so rickets from dietary phosphate deficiency is unusual. Dietary phosphate deficiency can be found in patients taking aluminum-binding antacids (which bind phosphate), or in patients on prolonged parental nutrition with inadequate phosphate, and in premature infants on breast milk without phosphate supplementation.

Rickets caused by a liver 25-hydroxylase deficiency is exceedingly rare since there appears to be several enzymes capable of carrying out this reaction. A loss-of-function mutation in the 25-OH-D-1-alpha-hydroxylase enzyme is termed pseudovitamin D-deficiency rickets (PDDR) or vitamin D-dependent rickets type I. There is hypocalcemia, hypophosphatemia, and hyperphosphatasia, and elevated PTH levels. Serum calcidiol levels are normal and calcitriol levels low and do not respond to administration of vitamin D. Treatment is with small doses of calcitriol (10-20 ng/kg/d). An inactivating mutation of the vitamin D receptor leads to resistance to calcitriol and is termed vitamin D-dependent rickets type II. Patients have the typical biochemical and radiographic findings of rickets, and their serum calcitriol and PTH levels are markedly elevated. Clinically patients also exhibit severe onset of bone deformities in infancy, alopecia, and growth retardation. Treatment consists of high dose calcitriol (up to 6 mcg/kg/d) and supplemental calcium (up to 3 gm/kg/d elemental calcium).

X-linked hypophosphatemic rickets is one of the most common causes (1:20,000 births) of rickets in developed countries. It is caused by an as yet unidentified phosphaturic agent produced possibly by osteoblasts. Serum calcium, PTH, calcidiol levels are normal, and there is marked hypophosphatemia and hyperphosphaturia. Calcitriol levels are inappropriately low. The primary agents employed in treatment are calcitriol (30-70 ng/kg/d) and elemental phosphorus (0.25-2 gm/kg/d in 4-6 divided doses).

Questions

1. True/False: The main biochemical findings in hypoparathyroidism are hyperphosphatemia and hypocalcemia.
2. True/False: Calcitonin injections can be used to raise a patient's serum calcium level.
3. True/False: Breast feeding prevents rickets.
4. True/False: Elevated levels of parathyroid hormone always result in hypercalcemia.
5. True/False: Vitamin D alone is curative all various forms of rickets.

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Answers to questions

1. True.
2. False. Calcitonin lowers serum calcium levels.
3. False. Breast milk contains low levels of vitamin D. Vitamin D supplementation will prevent rickets.

4. False. A compensatory increase in PTH in response to hypocalcemia (such as with rickets) will usually result in low or normal calcium levels. High PTH levels should result in hypercalcemia; however, pseudohypoparathyroidism is an end-organ resistance to PTH, so despite an elevated PTH, patients have hypocalcemia.

5. False. The mainstay of therapy in hypophosphatemic rickets is oral phosphate replacement. Calcitriol is used to decrease the amount of phosphate needed (increases intestinal phosphate absorption), and prevent hypocalcemia and secondary hyperparathyroidism.

Chapter XVI.1. Systemic Lupus Erythematosus
Kara S. Yamamoto, MD

A 14 year old female presents with a 6 week history of fatigue and facial rash. Her rash seems to be exacerbated by sun exposure. She has recently developed pain and swelling in her fingers and wrists. She has no significant past illnesses. Family history is significant for an aunt with lupus and a grandmother with thyroid disease.

Exam: VS T 37.8, P 88, R 20, BP 110/66. Height and weight are at the 20th percentile. She is alert and cooperative. She has thinning hair over her front scalp with some fine short hairs. She has an erythematous maculopapular rash over her malar areas spanning the bridge of her nose, erythema of the hard palate and a few shallow gingival ulcers. Joint exam reveals mild swelling and tenderness to palpation and range of motion in the proximal interphalangeal joints of several of her fingers and both wrists. Heart, lung, abdomen, back and neurological examinations are within normal limits.

Laboratory: WBC 2.5 with 87% segs, 5% lymphs, 6% monos, 2% basophils. Hgb 10. Platelet count 167,000. ANA 1280. ESR 45. Urinalysis without protein or blood. No cellular casts or significant red or white cells.

Systemic Lupus Erythematosus (SLE) is a multisystem, inflammatory disease of autoimmune origin, characterized by the production of auto-antibodies directed against elements of the cell nucleus. The disease is often chronic with episodic flares of disease and remissions (1).

The etiology of lupus is unknown and thought to be complex and multifactorial. Many lines of evidence point to both host (endogenous and genetic) and environmental (e.g., environmental exposures and infection) factors, which contribute to development of disease. Although numerous susceptibility foci and genetic linkages or associations have been reported, there is no predominant or single one identified. Genetic associations found in one race may not apply to other races or even subsets within a particular race. Genes which confer susceptibility to developing the disease may differ from individual to individual and may result in different clinical manifestations and severity of disease.

Family studies offer compelling evidence of genetic predisposition. Connective tissue disease other than SLE has been reported in 10% of families of patients with SLE (1). There is an increased risk of developing SLE in first degree relatives of patients with SLE (2). A person with SLE has increased risk of having a sibling with SLE versus the general population having a sibling with SLE (2,3). Twin studies show higher rates of SLE in monozygotic versus dizygotic twins (4).

Studies have suggested that lupus is more prevalent in non-Caucasian ethnic groups such as African-American, Hispanic, Asian, Native American Indian, Alaskan Indian and Indian populations, which lends support for there being some genetic basis for disease susceptibility. We recently reviewed pediatric lupus patients in our rheumatology clinic in Hawaii, demonstrating that children of Samoan, Filipino and Japanese ancestry have increased odds ratio of developing SLE (5).

Other factors such as ultraviolet radiation, stress, and infection may also play a role in pathogenesis. Drugs such as hydralazine, isoniazid, sulfonamides, penicillin, beta-agonists and anticonvulsants have been associated with "drug-induced" lupus which is dependent upon the presence of the drug.

The true incidence and prevalence of lupus is not known, but is generally thought to be lower in children than in adults. Lupus is most common in women of child bearing years, but about 20% or more of patients with SLE are children. Lupus is rarely seen before the age of 5 years, is more common after 9 to 10 years, and tends to cluster around the age of puberty. Female predominance of the disease is less pronounced before puberty.

Clinical manifestations of lupus can vary widely. Lupus can present with non-specific and milder symptoms over an extended period of time, but children typically have a more acute onset. Constitutional symptoms are common, such as fever, fatigue, decreased appetite, and weight loss. High fevers should be suspect for an underlying infection in patients with lupus who are immunocompromised due to their disease and the immunosuppressive medications they are on.

Rash is common and variable. The classic malar "butterfly" rash is usually symmetric, spanning the bridge of the nose, but sparing the nasolabial folds. The rash may be photosensitive and involve other sun exposed areas such as the forehead, ears and the "V" of the neck and upper chest. Rash may involve other parts of the body, including the palms of the hands. Most heal without scarring or pigmentation. Severe vasculitis or thrombosis may result in ulcerations or even gangrene. Discoid lesions, which often lead to scarring, atrophy, and pigmentation changes, seem to be less frequent in children. Nail bed involvement with periungual erythema may occur. Livedo reticularis may also occur. Alopecia is common and is associated with active disease. It often involves the frontal scalp and may be generalized or patchy. Mucocutaneous lesions may include vasculitis and ulceration of the hard palate, aphthous stomatitis, and less frequently ulcers or perforation of the nasal mucosa or septum.

Vasculitis affects small blood vessels in lupus. Children with lupus may have Raynaud's phenomenon, manifested as sequential color changes (blanching to cyanosis and hyperemia) in their distal extremities often related to exposure to cold or stress. It can vary in severity. Ischemia may lead to pain and ulcers, and in severe cases, atrophy, necrosis and gangrene. Treatment may include biofeedback, behavior modification, vasodilators, and nerve blocks.

Arthritis and arthralgias are common. Arthritis is usually transient and usually does not result in permanent deformity, although it can be quite painful. Occasionally it can be persistent and erosive. Patients with lupus, especially those requiring long term corticosteroid therapy, are at risk for avascular necrosis particularly in weight bearing joints.

Myalgia and even myositis may occur often related to vasculitis. Corticosteroid therapy may also contribute to corticosteroid myopathy with weakness.

Nephritis is one of the most common complications of lupus and affects about 75-80 % of children with SLE. It usually is manifested in the first 1-2 years of disease. Microscopic hematuria is common. Proteinuria, including nephrotic syndrome and hypertension may occur. Acute renal failure at presentation is rare. Renal histology on tissue obtained on a renal biopsy allows classification of the type of glomerulonephritis based upon the World Health Organization Classification of Renal Nephritis.

The most common cardiopulmonary manifestations are pericarditis and pleural effusions. Pulmonary hemorrhage and acute lupus pneumonitis can occur. Pulmonary infection is also frequently encountered. Myocarditis can occur. Myocardial infarction and valvulitis (Libman-Sacks endocarditis) are less frequent in children than adults.

Lymphadenopathy is quite common in children with SLE, sometimes associated with splenomegaly. Hepatomegaly can also be present.

Gastrointestinal complaints frequently occur in children with SLE. Serositis, pancreatitis or bowel vasculitis can occur. Bowel vasculitis can be complicated by hemorrhage, perforation, ischemia, or infarction. Corticosteroids may mask or suppress symptoms, making the diagnosis difficult.

Central nervous system involvement is a major cause of morbidity and mortality in children with lupus. Some estimate that up to 50% of children and adolescents with SLE have CNS involvement at disease onset. CNS involvement is variable in severity and manifestation. Symptoms may be subtle and difficult to detect or diagnose. CNS problems include neuropsychiatric manifestations, headache, seizures, cerebrovascular accidents, chorea, peripheral neuropathy, papilledema, visual loss, vertigo, myelopathy. Depression and difficulty with memory and concentration are common. Psychosis with hallucinations and paranoia may also occur. Cognitive impairment may cause a child to have difficulty with school. Headache is a common problem. Difficulty in coping with the disease, its manifestations and side effects of medications is common, particularly for adolescent patients.

Associated phenomenon may include antiphospholipid syndrome characterized by episodes of thrombosis, spontaneous recurrent abortions, cardiovascular crises, and menorrhagia. Thrombocytopenic purpura (TTP) and Evans' Syndrome (acute hemolytic anemia) has been seen in association with SLE. Sjogren's syndrome is rare in children (keratoconjunctivitis sicca, xerostomia). Autoimmune thyroid disease may occur in children with lupus.

Laboratory Evaluation

Antinuclear antibodies (ANA) are a hallmark of SLE and present in virtually all children with active SLE. The most specific pattern of nuclear immunofluorescence is "peripheral" suggesting the presence of ds-DNA (double stranded DNA), however the "homogeneous" pattern is the most common. The ANA is a very non-specific test and may be present in other diseases or children without rheumatic disease.

Anti-ds DNA antibodies are more specific for SLE and are often found in children with active SLE, particularly those with active nephritis. Antibodies to extractable nuclear antigens (ENA) may be useful. Anti-Sm antibodies (pronounced anti-Smith) are strongly associated with SLE. Antibodies to SS-A/Ro and SS-B/La are strongly associated with SLE, neonatal lupus, and Sjogren's syndrome. Anti-RNP antibodies (anti-ribonuclear protein) may be present in SLE, but in high titers are associated with mixed connective tissue disease. Antihistone antibodies are present in children with SLE and drug-induced SLE.

LE cell preparations and false positive tests for syphilis (i.e., VDRL and RPR) have largely been replaced by the tests above for proof of the immunologic disorder in diagnosing SLE.

Antiphospholipid antibodies may also be associated with lupus in children. Laboratory testing for lupus anticoagulant and/or anti-cardiolipin antibodies is useful. Positive anticardiolipin antibodies are responsible for the false-positive VDRL seen in lupus. Antiphospholipid antibodies can prolong the partial thromboplastin time (PTT). These antibodies are associated with thrombosis (paradoxical since one would expect an anticoagulant to do the opposite), thrombocytopenia, livedo reticularis, and recurrent miscarriages. They can also be seen without the presence of SLE. Rheumatoid factor is present in some children with SLE, but high titers may suggest the presence of an overlap syndrome.

Immune complexes are thought to play a major role in the pathogenesis of SLE, however due to problems with reproducibility of assays and variability in correlating with disease activity, measuring immune complexes is of limited utility.

Decreases in serum complement particularly C3, C4, and CH50 may reflect active disease and are important in assessing disease activity, especially lupus nephritis.

Hematologic abnormalities such as anemia are common. Anemia may be secondary to chronic disease (normocytic, hypochromic) or due to autoimmune hemolysis with a positive Coombs test. Hypersplenism and drug sensitivity may complicate the anemia. Leukopenia, especially lymphopenia, and immune thrombocytopenia frequently occurs. Some patients may initially present as idiopathic thrombocytopenic purpura (ITP) with a positive ANA, and later progress to SLE.

Acute phase reactants such as ESR are often increased during disease activity. This is a non-specific test, however, and cannot distinguish between flares of disease and infection.

Urinalysis may show abnormal urinary sediment in patients with glomerulonephritis, as well as proteinuria. Determinations of urine protein and creatinine excretion are helpful in assessing renal disease.

The diagnosis of SLE is based upon clinical and laboratory findings. Classification criteria for SLE from the American College of Rheumatology, revised in 1982 have also been widely used for diagnosis (8). In adults, the presence of 4 out of 11 criteria are required for diagnosis with a sensitivity and specificity of 96% percent. In children, one study reported a sensitivity of 96% and a specificity of 100%, as compared with a rheumatic disease control group (7). The 11 criteria are: malar rash, discoid rash, photosensitivity, oral ulcers (oral or nasopharyngeal ulceration), arthritis, serositis (pleuritis or pericarditis), renal disorder (persistent proteinuria, cellular casts), neurologic disorder (seizures or psychosis), hematologic disorder (hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia), immunologic disorder (positive LE cell preparation, anti-DNA antibodies, anti-Sm antibodies, or false positive serologic test for syphilis), and antinuclear antibody.

Treatment

Corticosteroids (glucocorticoids) are indicated for the treatment of SLE with major organ involvement. Intravenous methylprednisolone may be useful in certain patients, particularly those with severe disease. Treatment is usually on a long term basis with tapering over a prolonged period of time raising concerns over potential complications such as growth suppression, susceptibility to infection, hyperlipidemia, hypertension, hyperglycemia, psychosis, myopathy, osteoporosis, cataracts, increased intra-ocular pressure, glaucoma, gastric irritation and Cushing's syndrome. Other effects may include hirsutism, acne, striae, and weight gain.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may be used to manage musculoskeletal complaints, but may not be appropriate in children with renal disease. Hydroxychloroquine is an antimalarial which may be helpful as an adjunct to corticosteroid therapy and may allow tapering of the corticosteroids. It can be useful for treatment of the arthritis and rash of SLE. Children taking this medication should be closely monitored for retinal toxicity.

Immunosuppressive agents such as cyclophosphamide, azathioprine, methotrexate, cyclosporin, and mycophenolate mofetil have been used to treat SLE. Cyclophosphamide pulsing (intravenous) is important in the treatment of severe SLE, particularly lupus nephritis and CNS disease. It has contributed to the increased survival of patients with nephritis. Toxicity may limit use, particularly concerns over the increased risk of infertility, infection, and malignancy. The role of plasmapheresis in treating lupus is not well defined, although it has been used in severe life threatening disease.

Course of the disease

Over the past 30 years or so, the life expectancy of children with SLE has significantly increased. Improvements in therapy, monitoring, and supportive care have all contributed to this improvement. Long term quality of life and outcomes have become increasingly important. The course of lupus in any child is unpredictable and varies from individual to individual. Most have chronic disease with disease remissions and exacerbations, although some patients may remain in remission for long periods of time. Close monitoring and follow up is essential to prevent significant morbidity and mortality.

Infection is the one of the major causes of morbidity and mortality in children with SLE. Infection has surpassed renal disease as the most common cause of death. Children with SLE are susceptible to infection as a consequence of both the disease and therapy, particularly corticosteroids and other immunosuppressive agents.

Growth abnormalities due to lupus and long-term corticosteroid therapy may result in short stature and delayed onset of puberty. Corticosteroids may cause cushingoid facies, hirsutism, and increased appetite leading to significant weight gain. These factors may have significant impact on children and especially adolescents, who are often very concerned about body image and peer acceptance.

Many patients experience difficulty in coping, psychological distress, and even depression with their SLE and complications relating to the disease and therapy. This can complicate assessment of neuropsychiatric problems secondary to central nervous system lupus. Neuropsychiatric deficits can adversely impact a child or adolescent's functioning and quality of life. Mental health services can play an important role in positive outcomes.

With the improved survival of children with SLE, cardiovascular complications are becoming an important problem of the illness. Abnormal lipid metabolism, long term complications of corticosteroid therapy, hypertension, and cardiac involvement secondary to lupus may all be contributing factors.

Avascular necrosis is also a problem with childhood SLE. This can occur with or without long term corticosteroid treatment and may result in significant pain and disability, even requiring joint replacement. The availability of alternate immunosuppressive therapies to corticosteroids may help decrease the incidence of this complication. Potential ophthalmologic complications from SLE and treatment with drugs such as hydroxychloroquine and corticosteroids require monitoring by an ophthalmologist.

Sun avoidance and protection is important in management of SLE. Many patients are photosensitive resulting in exacerbation of their rash. UV rays from other sources besides sunlight, such as fluorescent and halogen lights can also aggravate lupus. Sunscreen, protective clothing, and other devices to block UV emissions are helpful. A well balanced and nutritious diet, physical rest, and reducing emotional stress are also important in maintaining health.

The outlook for children with lupus has markedly improved. The continuing development of new treatments, improved surveillance of disease activity, and advances in supportive care promise to further enhance not only survival, but the quality of life for these children. Early diagnosis and prompt, aggressive treatment are also important in managing the disease and its complications.

Questions

1. List at least 6 of the 11 diagnostic criteria for SLE.

2. Name 3 drugs which are used for the treatment of SLE.

3. Which of the following statements are false?
   a. Leading causes of morbidity and mortality for children with SLE are infection, renal disease, and CNS involvement.
   b. ANA, anti-ds DNA antibodies, anti-Sm antibodies are part of the criteria for diagnosis of lupus
   c. Ophthalmologic complications are infrequent in children with SLE
   d. UV emissions may exacerbate lupus

4. True/False: A positive ANA test is a useful screening test for SLE?

5. True/False: Patients with a lupus anticoagulant have a prolonged PTT and they have hemorrhagic tendencies similar to patients with hemophilia.

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Answers to questions

1. Malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurologic disorder, hematologic disorder, immunologic disorder, antinuclear antibody

2. Corticosteroids, NSAIDs, hydroxychloroquine, cyclophosphamide, azathioprine, methotrexate, cyclosporine, and mycophenolate mofetil

3.c. Retinal toxicity may be a complication of hydroxychloroquine therapy. Long-termed corticosteroid therapy may be complicated by cataracts, glaucoma, and increased intra-ocular pressure. Rare cases of orbital/ocular vasculitis may occur.

4. The answer is true, depending on your interpretation. The ANA test is non-specific in that a positive ANA test by itself is not diagnostic of SLE. The ANA is frequently positive in normal individuals. However, a screening test is not a diagnostic test, but it is just used to screen. A negative ANA suggests that the patient does not have SLE. The answer to this question true, but it should be noted that the ANA is frequently ordered excessively and inappropriately.

5. False. It is true that patients with a lupus anticoagulant have a prolonged PTT. However, the lupus anticoagulant paradoxically is associated with and increased risk of thrombosis, rather than hemorrhage.

Chapter XVI.2. Juvenile Rheumatoid Arthritis

Kara S. Yamamoto, MD

This is a 4 year old female who has been limping with swelling of her right knee for several months. Her parents note that she cannot fully extend her right knee. She sometimes does not want to walk in the morning, but seems fine later in the morning and the rest of the day. Her past medical history is unremarkable. Physical examination demonstrates swelling (effusion) of her right knee, flexion contracture of 10 degrees and flexion to 120 degrees. No increased heat or pain upon range of motion is present. She appears unconcerned about her limp and swelling. Labs: WBC 8,600 with 45 polys, 47 lymphs, 8 monos. Hgb 12. ESR 20. UA normal. Rheumatoid factor negative, ANA 1:640 speckled.

Juvenile rheumatoid arthritis (JRA) is a chronic arthritis of childhood comprised of several different subgroups. It is one of the most common rheumatic diseases of childhood. Because the majority of children are rheumatoid factor negative, it is also known as juvenile idiopathic arthritis or juvenile chronic arthritis. Although the true incidence and prevalence of JRA are unknown, its incidence is estimated at 2 to 20 per 100,000 children per year based on the American College of Rheumatology (ACR) criteria (1,2).

Neither the etiology nor risk factors of JRA have been identified. It is considered to be an autoimmune disease. Chronic synovitis, T-cell abnormalities, abnormal immunoregulation and cytokine production, autoantibodies, immune complexes, and complement activation suggest that cell mediated and/or humoral processes are involved. Infection may have a possible role in developing JRA.

Complex and probably multi-factorial genetic factors are likely to play a role in the genetic predisposition to developing JRA as is evidenced by associations with HLA genetic polymorphisms which have been identified in some patients with JRA (3). There may also be associations with other autoimmune diseases such as insulin-dependent diabetes mellitus and autoimmune thyroiditis.

Currently there is no universal consensus on the classification of JRA. Several distinct subgroups have been suggested. The American College of Rheumatology criteria require that the age at onset of arthritis be less than 16 years, and that arthritis be present in one or more joints for at least 6 weeks. Other causes must be excluded. The onset type of JRA is determined by the first six months of disease and includes pauci- or oligo- articular JRA, polyarticular JRA, and systemic-onset JRA (4). The ACR criteria do not include seronegative spondyloarthropathies and related diseases (juvenile ankylosing spondylitis, juvenile psoriatic arthritis, and arthropathies associated with inflammatory bowel disease). More inclusive classification criteria such as the EULAR (European League Against Rheumatism) and ILAR (International League of Associations for Rheumatology) are also used. This chapter will describe the following subgroups:

A. Pauci-articular JRA
   1) Early childhood onset
   2) Late childhood onset
B. Polyarticular JRA
   1) Rheumatoid Factor Seronegative
   2) Rheumatoid Factor Seropositive
C. Systemic-onset JRA
D. Juvenile Psoriatic Arthritis

Arthritis is characterized by synovial tissue inflammation including hypertrophy of the synovium and increased secretion of synovial fluid. Affected joints may be warm, stiff or painful, swollen, limited in range of motion, and occasionally erythematous. Two or more of these signs is necessary for the diagnosis of arthritis (5). Synovial fluid analysis is not specific for JRA and may show an elevated total white count that is predominately polymorphonuclear neutrophils and mononuclear cells, and glucose levels may be decreased. The clinical course of the various subtypes of JRA is diverse. Depending upon the type of JRA, the degree of destruction of synovium and surrounding structures is variable. Rheumatoid factor positive disease tends to be more destructive, whereas the synovitis of seronegative JRA may not cause joint destruction, even after persistent activity.

JRA may involve other organ systems besides the joints depending upon the type of onset. Iridocyclitis/uveitis may be present in all subtypes of JRA, but especially in the pauci-articular disease of early childhood. All children with JRA should have regular ophthalmologic examinations including slit-lamp examinations. Rheumatoid factor positive JRA may demonstrate rheumatoid nodules and vasculitis. Systemic onset disease can develop multiple systemic manifestations. Growth retardation or limb length discrepancies can complicate the course of children with JRA.

Pauci-articular JRA describes the involvement of 4 or fewer joints and affects an estimated 40-60% of children with JRA. At least two distinct subgroups have been identified: Early childhood onset (frequently associated with positive anti-nuclear antibodies and iridocyclitis) and late childhood onset. Some classification criteria further divide early childhood onset into oligoarthritis and extended oligoarthritis.

Early childhood onset pauci-articular JRA affects predominantly girls under the age of 6 years. More common in Caucasian children, it accounts for about 30-40% of patients with JRA. About 50% have monoarticular arthritis. Large joints of the lower extremities are most often involved, including knees and ankles, occasionally elbows. This subtype is associated with positive ANAs

(anti-nuclear antibodies) and chronic iridocyclitis. It has been estimated that up to 30% of these children have a risk of chronic iridocyclitis/uveitis in the first several years of disease. Eye involvement is usually insidious with few if any symptoms or signs. These patients require routine slit-lamp examinations to detect early inflammatory changes. Late sequelae of chronic iridocyclitis include posterior synechiae, band keratopathy, cataract formation, glaucoma, visual loss or blindness. Hips are infrequently affected. These children are not systemically ill and usually function well without a great deal of pain. There is a subset of these children who initially present as pauci-articular in the first 6 months of disease, but progress to poly-articular disease thereafter (extended oligoarthritis).

The late childhood onset subgroup of pauci-articular JRA is associated with HLA B27 and development of enthesitis and sacroiliitis. The terms Juvenile Spondyloarthropathy or Juvenile Ankylosing Spondylitis have also been used. It is usually oligoarticular at onset and affects approximately 10-15% of children with JRA. There is a male predominance with the age of onset usually after 8 years of age. The onset of arthritis can be insidious or acute. The clinical course may be episodic and variable resulting in little to significant joint destruction. It often affects the large joints of the lower extremities (hips, knees, ankles). Frequently these patients develop enthesitis (swelling along tendons and at sites of tendonous/ligamentous insertion into the bone). Achilles enthesitis is common. Tarsal involvement may occur. A subset of children who initially present with only enthesitis later develop arthritis. Some patients develop acute iridocyclitis (eye pain, red eyes and photophobia). Although usually absent at onset, some patients develop thoracic and lumbar spine involvement with loss of flexion meeting criteria for ankylosing spondylitis. HLA-B27 is present in about 80% of these children. A family history of spondyloarthropathy such as ankylosing spondylitis, Reiter's disease, inflammatory bowel disease with spondylitis, psoriatic arthritis, and acute iridocyclitis is often obtained.

Polyarticular JRA affects approximately 35% of children with JRA. It can be further sub-divided into Rheumatoid factor positive (seropositive) and Rheumatoid factor negative (seronegative) disease.

The seronegative JRA subtype typically presents at less than 5 years of age, although it may occur at any age during childhood. There is a female predominance. It occurs in 20-30% of patients with JRA and is characterized by a negative test for IgM rheumatoid factor. Symmetric involvement frequently occurs, most commonly in the large joints. The small joints of the hands and feet may also be involved. Cervical spine involvement with limitation of range of motion in the neck and temporomandibular joint involvement are common. Micrognathia may be noted with time. Boutonniere deformities and flexion contractures occur more frequently than swan-neck deformities. Leg length discrepancies, angular deformities and brachydactyly may occur. Morning stiffness and gelling or stiffness after inactivity are frequent. Patients are usually not systemically ill, but low-grade fever, mild anemia, mild lymphadenopathy and hepatosplenomegaly may occur. These children often respond well to therapy and can have little joint destruction despite a number of episodes over several years. Recurrent episodes may tend to cause progressive joint damage and deformity. Uveitis occurs in about 10% of these children and regular ophthalmology examinations are important.

The seropositive JRA usually occurs in children over the age of 8 years with a female predominance. It occurs in 5-10% of patents with JRA and is likely the equivalent of adult rheumatoid arthritis (RA). Like RA in adults, it is frequently an aggressive, destructive and erosive joint disease with joint destruction occurring within 1 year of onset. It can have a poor prognosis with high risk of permanent joint disability and compromised functioning. Early and aggressive therapy is necessary to prevent poor outcomes. It is characterized by extra-articular manifestations such as rheumatoid nodules (sub-cutaneous nodules often found over pressure points such as the elbows, heels, knuckles and extensor surfaces of the finger, and the first metatarsophalangeal joints). Rheumatoid vasculitis resulting in ulcerative lesions may be seen. Felty syndrome (splenomegaly with leukopenia) or Sjogren syndrome (parotitis, dry eyes and mouth) are occasionally noted, but more often in adult disease.

Systemic-onset JRA, also sometimes known as Still's disease, is characterized by high, intermittent fevers and other organ system involvement. It affects about 10% of children with JRA, occurring equally in males and females. It often begins before 5 years of age, but can occur throughout childhood into adult life. Fevers of 39.4 degrees (103 F) or higher occur once or twice a day with interim normal or even subnormal temperatures. Fevers tend to occur in the evening, sometimes also in the mornings. Fevers may last from weeks to months. Most patients develop a characteristic, transient rash often described as salmon pink, or red and maculopapular. The rash can occur anywhere on the body and often accompanies the fever. It may occasionally be pruritic. Some patients will also develop lymphadenopathy and hepatosplenomegaly. Pleuritis and pericarditis may occur in up to 50% of patients, for which symptoms may include chest pain and difficulty breathing, although many may be relatively asymptomatic. Rarely, myocarditis may occur. Abdominal pain may occur. Laboratory findings often include an elevated peripheral white blood cell count, sometimes with a left shift, anemia and elevated platelet counts. Mild transaminase elevations or hyperbilirubinemia may be noted. Occasionally severe anemia or disseminated intravascular coagulation and severe hepatic dysfunction may occur. Iridocyclitis is usually absent. Recurrent systemic episodes occur in up to 50% of these children. Children often complain of myalgias and arthralgias. Arthritis may not develop until sometime into the course of the systemic manifestations. These children are often first seen for evaluation of fever of unknown origin and go through the process of eliminating other causes of fever from the differential. Many of these children will develop persistent arthritis within the first few months of onset, although arthritis developing years after the initial febrile episode have been reported. Arthritis is variable and may be polyarticular affecting both small and large joints. Chronic polyarthritis may become the primary problem.

Juvenile psoriatic arthritis affects males and females equally. These children are usually Caucasian. Arthritis often presents asymmetric and oligoarticular with small and large joint involvement. The toes are often involved. Dactylitis is common. Isolated DIP involvement or spondylitis may occur. Other associations include chronic uveitis and nail pitting. Psoriasis or a family history of psoriasis are needed for the diagnosis. ANA may be positive and HLA-B27 is present in about a third of these children. RF is negative.

The diagnosis of JRA depends upon a comprehensive history and physical examination demonstrating the presence of chronic arthritis for at least 6 weeks and exclusion of other conditions. There is no "diagnostic test" for JRA. Laboratory studies may reflect changes consistent with inflammation, but are not diagnostic. Some children have normal labs despite active arthritis. A positive rheumatoid factor in the presence of chronic arthritis and a pattern of disease helps to make a diagnosis in the small percentage of children who have seropositive disease. ANAs are strongly associated with early childhood-onset pauciarticular JRA and chronic iridocyclitis. HLA B27 is strongly associated with spondyloarthropathies, but can also be found in a number of healthy individuals. It is useful if a child presents with history and clinical findings consistent with JRA or spondyloarthropathy, since this may help in classification. X-rays, other imaging tests, joint synovial fluid aspiration and synovial biopsy may be helpful, especially in excluding other conditions. X-rays help detect joint changes, including atlantoaxial subluxation in children with cervical spine involvement. Joint aspiration and biopsy are particularly helpful in monoarticular arthritis where the differential is much broader than for polyarticular arthritis.

The list of differential diagnoses causing arthritis or arthropathy is large. Some of these are as follows. Infection related arthritis must be considered in the differential of JRA, including septic arthritis, viral arthritis, toxic synovitis, Lyme disease, reactive arthritis, and osteomyelitis. In Hawaii, acute rheumatic fever (ARF) must be included in the differential particularly in patients of Polynesian descent,

who seem to have a predisposition to developing ARF. Malignancy such as leukemia, neuroblastoma, lymphoma, Hodgkin disease, rhabdomyosarcoma and bone tumors may cause frank arthritis or musculoskeletal complaints that mimic arthritis. Trauma must also be considered. Other autoimmune diseases such as systemic lupus erythematosus and dermatomyositis can present with joint pain and/or arthritis, but are often associated with other systemic symptoms. Other vasculitides such as Henoch-Schonlein purpura and Kawasaki disease usually have other extra-articular manifestations in addition to arthropathy.

The differential diagnosis of joint pain may also include growing pains, fibromyalgia, psychogenic pain, avascular necrosis syndromes, osteochondroses (Osgood-Schlatter), enthesitis, patellofemoral or chondromalacia patella syndrome, discitis, and inherited or congenital syndromes. Hypermobility due to either benign hypermobility syndrome, Ehlers-Danlos syndrome or other connective tissue defects such as Marfan syndrome can also cause joint pain and sometimes swelling.

The goals of therapy are to control pain and inflammation; to prevent joint damage; to preserve range of motion and muscle strength; strive for normal function, growth, nutrition, physical and psychosocial development; and to control systemic manifestations. Treatment depends upon many considerations including a child's individual clinical manifestations, overall prognosis, the child and family's social situation, the child's functionality and extent of joint deformity. A multi-disciplinary team approach is essential in optimizing results. Physical therapy and occupational therapy are important for some patients. Orthopedic surgeons may also help in management. Patient and family understanding and participation in management are important. Education of the patient and family is vital and should include the disease, findings, prognosis, outcomes, medications, monitoring, and ancillary therapies. Patients and families need to be supported. Children should be encouraged toward normal play, except for those activities which may damage inflamed joints. Bicycle riding and swimming are usually good activities to avoid too much stress on involved joints.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are important initial agents in the treatment of JRA. In the United States these include naproxen and ibuprofen. Tolmetin is approved for use in children, but is used less frequently. A number of other have been used, but may not be approved for use with JRA in children. Salicylates can also be very effective; however concerns about salicylate toxicity and the association with Reye syndrome have decreased its usage in the United States. Cox-2 specific inhibitors are being evaluated for use in children. It may be necessary to try two or more NSAIDs sequentially as some patients may respond better to one agent versus another. There is no way to predict which patient will respond better to which agent, although it may be useful to try different chemical classes of NSAIDs. In addition to the arthritis, NSAIDs may also help the fever and some of the other manifestations of systemic-onset JRA. They may also have some effect on the iridocyclitis of JRA. NSAIDs can be associated with gastrointestinal side effects, even gastritis or ulcer disease. Renal and hepatic toxicity can occur. A child who is dehydrated or has renal disease is at increased risk for renal toxicity. Headaches or behavior changes have been noted. Pseudoporphyria with photosensitivity has been reported, particularly with naproxen. NSAIDs can also interfere with platelet function and cause prolonged bleeding.

Controlled studies in small numbers of patients have shown that hydroxychloroquine, oral gold salts, and D-penicillamine are not more effective than placebo (6). However, hydroxychloroquine is sometimes used as an adjunct for the treatment of JRA in older children. Ophthalmological exams every 6 months are necessary to monitor patients on hydroxychloroquine since retinopathy can occur. IM gold is used less frequently since the introduction of methotrexate, perhaps in part due to the requirement of weekly injections, the need for close monitoring, and the potential for serious side effects.

Methotrexate is an effective agent in children with severe JRA and is frequently used to treat children who have failed to respond to NSAIDs. Its once a week dosing (parenteral or oral) may help with compliance. Side effects can include bone marrow suppression, gastrointestinal symptoms, alopecia, dermatitis, oral ulcers, headache, acute interstitial pneumonitis, and pulmonary fibrosis. Hepatic fibrosis or cirrhosis is a rare finding in children.

Sulfasalazine may be effective in treatment of JRA, although drug toxicity may be a problem. Side effects include gastrointestinal irritation, dermatitis, oral ulcerations, bone marrow suppression and hepatic toxicity. Sensitivity to salicylates or sulfa, impaired hepatic or renal function, porphyria or glucose-6-phosphate dehydrogenase deficiency are contraindications to its use.

Glucocorticoids may be useful in the short-term treatment of severe systemic disease, severe JRA refractory to other therapies, and iridocyclitis. It is usually used in conjunction with other anti-inflammatory or anti-rheumatic medications. It is desirable to avoid prolonged use because of complications such as growth retardation, osteopenia/osteoporosis, infection, fractures and cataracts. Intravenous pulse dosing of corticosteroids may be helpful in some patients with more severe disease, such as systemic onset arthritis. Intra-articular glucocorticoids may be a therapeutic option in JRA, particularly when activity persists in a few joints despite treatment. Simultaneous injection of multiple joints may also be useful in certain cases.

New biologic agents targeted against TNF-alpha and IL-1 have been approved for use in adult RA and are being studied in children. TNF-alpha antagonists have been studied for use in older children with certain types of JRA.

Immunosuppressive and cytotoxic agents have been used in life-threatening disease or severe progressive arthritis. IV gamma globulin has been used with mixed results and its role in the treatment of JRA is unclear. Autologous stem cell transplantation is also being evaluated in a small number of children with severe disease.

Prognosis varies with the onset type or subtype and clinical course. However, studies indicate that many children with JRA are without serious disability and are able to work and function normally. Amyloidosis is a cause of mortality in some parts of the world, but is very rare in the United States. Even systemic-onset JRA is rarely fatal with our current therapies. The highest risk of morbidity appears to be children with systemic-onset disease and seropositive disease. Iridocyclitis can cause serious disability. Some children who develop spondyloarthropathy may have a more severe course, but their prognosis is fairly good.

Questions

1. Which of the following tests has a high positive predictive value for JRA
    a. erythrocyte sedimentation rate
    b. C-reactive protein
    c. HLA-B27
    d. antinuclear antibody
    e. white blood count

2. True/False: JRA is largely a clinical diagnosis.

3. True/False: All patients with suspected JRA should be referred to an ophthalmologist for a thorough eye examination.

4. Name three types of JRA and how are they different.

5. List some pharmacologic treatments for JRA that have been used or are being studied.

6. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit inflammation, reduce fever and reduce pain. Theoretically, how does the action of NSAIDs in treating JRA differ from the action of NSAIDs treating an ankle sprain?

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Answers to questions

1. None of these answers are correct. None of these tests have a high positive predictive value for JRA.
2. True.
3. True. Iridocyclitis may be difficult to diagnose by a non-ophthalmologist.
4. Polyarticular, pauci-articular, systemic JRA. Refer to the chapter for how they are different.
5. NSAIDs, Cox-2 inhibitors, hydroxychloroquine, oral gold, D-penicillamine, methotrexate, sulfasalazine, glucocorticoids, TNF-alpha antagonists, IV gammaglobulin.
6. In JRA, NSAIDs inhibit an inflammatory reaction which is pathological and destructive. The inflammation which occurs in an ankle sprain is largely a repair process. The benefit of using NSAIDs to inhibit this type of inflammation is less clear.

Chapter XVI.3. Vasculitis
Donald A. Person, MD

This is a five year old boy who presents to the Emergency Department with acute right ankle arthritis. His ankle is red, hot, tender, and obviously swollen. His mother states that he refuses to bear weight on that leg. She further notes that he complained of left knee pain the previous day and that he has not been himself since an upper respiratory infection a week previously. He is anorexic and has lost 2-3 pounds over the past week, thought to be due to recurrent, crampy abdominal pain.

Past medical history and family history are noncontributory.

Exam: VS T 39, HR 160, RR 24, BP 130/90. He is ill-appearing, irritable, and febrile. HEENT exam is positive for mild pharyngitis. His neck is supple. His chest shows some pre-sternal edema with clear lungs and a gallop rhythm. Abdomen: His liver is tender to deep palpitation and percussion. Borborygmus is auscultated. Genitalia: Circumcised male with bilaterally descended testes. There are extensive ecchymoses on his scrotum with swollen, weeping red involvement of the corona of the glans penis. He may have a borderline effusion of his left knee and 2+ swelling, erythema, tenderness, pain-on-motion and limitation-of-motion of the right ankle. His skin exam is positive for slightly raised petechial rash on his legs, most prominent on his ankles, posterior thighs and buttocks. Some lesions have coalesced into ecchymotic purpura.

Laboratory: CBC WBC 36,600, Hgb 8.2, Hct 26, platelet count 750,000. UA: cloudy, amber; sp gr 1.029, blood 3+, protein 2+, rbc casts 2-3 per hpf, and granular casts 1-2 per hpf. Erythrocyte sedimentation rate, 90 mm/hr. ANA, negative, RF, negative, ASO 250 Todd units, IgG 1280, IgM 280, IgA 600 mg/dl. Blood and urine cultures were negative. Stool guaiac 2+. Uric acid 6.5mg/dl, BUN 30mg/dl, Cr 1.3mg/dl, SGOT 90, SGPT 110. A skin biopsy demonstrates leukocytoclastic vasculitis on light microscopy and IgA staining of the vascular endothelium on fluorescent microscopy.

This patient has perhaps the most common vasculitis of childhood, namely Henoch-Schonlein purpura (HSP, also called anaphylactoid purpura or rheumatoid purpura).

The vasculitides of childhood are a complex and poorly understood group of inflammatory conditions whose etiologies appear to be on an immune basis. Several classification schema have been proposed based on: 1) vessel size, 2) presumed immunopathophysiology, or 3) organ involvement. The more common vasculitides are listed below:

I. Small and Medium Vessel Vasculitis
   A. Immune Complex Mediated
      1. Henoch-Schonlein Purpura
      2. Hypersensitivity vasculitis
      3. Polyarteritis nodosa (PAN)
      4. Urticarial vasculitis
      5. Cryoglobulinemia
      6. Connective tissue diseases (SLE, JRA, dermatomyositis, scleroderma, Behcet disease)
   B. Antineutrophil Cytoplasmic Antibody (ANCA) Associated Disorders:
      1. Wegener's granulomatosis*
      2. Microscopic polyarteritis
      3. Churg-Strauss syndrome*
      4. Drug-induced vasculitis
   C. Miscellaneous
      1. Erythema elevatum diutinum
      2. Paraneoplastic*
      3. Infection
      4. Inflammatory bowel disease
II. Large vessel vasculitis
   A. Temporal arteritis*
   B. Takayasu arteritis

*rare in childhood

Henoch-Schonlein purpura (HSP) is characterized by a tetrad including: palpable purpura, arthritis, abdominal pain and glomerulonephritis. The rash of HSP has been described as palpable purpura. Certainly petechiae are very common early and often tend to coalesce. Target lesions, ecchymosis, lymphangitic streaks and purple or bloody suffusions are sometimes seen. The distribution of the rash is typically from the waist down. Occasionally the rash involves the upper extremities and I have seen the rare child with a generalized rash of the entire body to include involvement of palms, soles, and even the scalp. Histopathologically, leukocytoclastic vasculitis is observed and immunopathologically, IgA is deposited in involved vessel walls and the renal glomerulus. In spite of there being two subtypes of IgA (i.e., IgA1, IgA2) only IgA1 is involved in HSP. Arthritis is often extremely acute and may be quite inflammatory. Large joints of the lower extremities are most commonly involved, especially ankles and knees. The arthritis is much like that of acute rheumatic fever, often very acute, sometimes migratory and often, exceedingly responsive to nonsteroidal anti-inflammatory drugs (NSAIDs). Hypertension usually responds to diuretic therapy and judicious fluid management. Renal involvement is relatively mild to moderate and is of the nephritic type. Occasionally, a nephrotic syndrome may occur instead. The gastrointestinal tract is commonly affected and most often, crampy abdominal pain is the primary manifestation. Diffuse bleeding from the GI tract is treated medically. Rarely intussusception complicates the picture and obstruction or perforation may necessitate emergency surgery. Testicular vasculitis maybe confused with testicular torsion. Corticosteroids must be reserved for serious complications of the disease and should not be instituted for treatment of the rash or arthritis. Mild recurrent abdominal pain likewise is best managed conservatively.

Polyarteritis nodosa (PAN) was the first described vasculitis and it is a prime example of medium vessel vasculitis. Although occasionally seen in children, it is distinctly far more common in adults. Infantile polyarteritis nodosa (IPAN) is a rare and often lethal inflammatory disease of small and medium-sized arteries. Clinically, IPAN is often considered part of the spectrum of Kawasaki Disease

(KD), in spite of the fact that IPAN was described nearly 130 years ago. Specifically, IPAN, with aneurysmal involvement of major coronary arteries and fatal KD are clinically and pathologically indistinguishable. Indeed, the primary distinction between KD and IPAN is that the diagnosis of KD is based entirely on clinical criteria while the diagnosis of IPAN is based on histologic findings. Additionally, a major distinction between polyarteritis and KD is the profound difference in prognosis; much worse for IPAN.

Microscopic polyarteritis is a necrotizing vasculitis, which affects small vessels (capillaries, venules and arterioles) in the kidneys and lungs. It is commonly associated with the presence of circulating antineutrophil cytoplasmic antibody (ANCA). Clinically, necrotizing glomerulonephritis occurs in the majority of patients. Hemoptysis and life-threatening pulmonary hemorrhage may supervene. This vasculitis is distinguishable from Wegener's granulomatosis in that respiratory tract symptoms are less and granulomatous inflammation is not present in microscopic polyarteritis.

Hypersensitivity vasculitis: Cutaneous involvement includes palpable purpura, papules, urticaria, erythema multiforme vesicles, pustules, ulcers and necrosis. Typically the rash involves dependent regions and occurs in crops. The patient is usually asymptomatic, but occasionally complains of burning/tingling. With regard to treatment, one must: 1) exclude systemic involvement, and 2) identify and remove offending allergens/agents, most often medications.

Urticarial vasculitis is an entity with three subtypes which have been described: normocomplementemic; hypocomplementemic, and the hypocomplementemic urticarial vasculitis syndrome (HUVS). The latter disease resembles systemic lupus erythematosus (SLE). The skin involvement is by definition, urticarial. Those patients with the lupus-like syndrome may require corticosteroid treatment and those with normal complement levels are usually self-limited.

Cryoglobulins are antibodies that precipitate in the cold and resolubalize on warming. Cryoglobulinemic vasculitis is associated with autoimmune conditions in childhood. Cryoglobulins may contain IgA, IgG or IgM, some have rheumatoid factor activity and they have been classified into types I, II and III. Types II and III may be associated with vasculitic syndromes. Immune complexes of mixed cryoglobulins, deposit in vessel walls, activate complement and produce recurrent palpable purpura with cutaneous ulceration. Hepatis C virus infections account for the majority of cases.

Vasculitis complicates several of the connective tissue diseases of childhood. These would include systemic lupus erythematosus juvenile rheumatoid arthritis, dermatomyositis, scleroderma, and Behcet disease. Clinically the vasculitic manifestations may be as minimal as a purpuric skin rash in SLE to telangiectasis of the nail beds in dermatomyositis to necrosis and gangrene of one or more digits to life threatening central nervous system vasculitis.

Wegener's granulomatosis or lethal midline granuloma is a rare vasculitis characterized by a triad of necrotizing vasculitis of the upper respiratory tract, the lower respiratory tract and focal segmental glomerulonephritis. Patients present with fever, malaise, weight loss, arthralgias, myalgias, rhinitis, sinusitis, nasal and oral ulceration. Pulmonary symptoms include dyspnea, chest pain, bloody sputum, and hemoptysis. A majority of patients develop antineutrophil cytoplasmic antibodies (ANCA) have been recognized since 1985 and are classified as cytoplasmic (c) or perinuclear (p) depending on the fluorescence location. ANCAs may have some diagnostic and prognostic significance. A tissue diagnosis is required to differentiate this condition from another rare vasculitis, lymphomatoid granulomatosis, perhaps more prevalent in children than Wegener's.

Churg-Strauss syndrome was initially reported under the descriptive title of allergic granulomatosis and angiitis. Churg-Strauss syndrome is virtually non-existent in children.

Takayasu arteritis is the prototype vasculitis involving large vessels. Takayasu arteritis (also known as pulseless disease of Japan) involves the aorta and its branches. It is exceedingly uncommon in children; however it is seen in teenagers from Micronesia and should always be considered in an adolescent girl with severe hypertension and a peripheral or abdominal bruit. Non-specific symptoms such as malaise and arteralgia (pain over blood vessels) are seen early on as the disease progresses. The involved vessels progressively narrow producing inequality in pulses, claudication and ischemia. The diagnosis should be suspected in young women with a systemic inflammatory illness, altered arterial pulses, or bruits. The diagnosis is confirmed by angiography and in our recent experience, treatment is often accomplished by interventional radiology/angiography procedures such as angioplasty.

The terms "purpura", "petechiae", and "ecchymosis" are frequently used in the clinical descriptions of vasculitic and other conditions. Note that in HSP, the term purpura is preferred over ecchymosis although the dictionary definition of these terms are the same or almost the same. The implied difference is that purpura have a sharply demarcated border and imply that vasculitis is the etiology, while ecchymosis has a diffuse border which implies that trauma or a hemorrhagic diathesis is the etiology. In HSP, the lesions are sharply demarcated (i.e., a vasculitis) which clinically appears as petechia (smaller lesions) and purpura (larger lesions). Compare this to idiopathic thrombocytopenic purpura (ITP), in which these lesions can be sharply demarcated resembling petechia and purpura, but ultimately, they develop frank bruising (i.e., ecchymosis). HSP is a vasculitis, while ITP is not.

Questions

1. Which immunoglobulin is prominently involved with the lesions of Henoch-Schonlein purpura?
2. What is the tetrad of Henoch-Schonlein purpura?
3. What histopathological term is used to describe the light microscopic findings in the skin biopsy of HSP?
4. Infantile polyarteritis nodosa (IPAN) is considered by some to be the severe end of the spectrum of which other vasculitis of childhood?
5. Name three connective tissue diseases of childhood, which are sometimes complicated by vasculitis.

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Answers to questions

1. IgA.
2. purpura, arthritis, abdominal pain and glomerulonephritis.
3. leukocytoclastic vasculitis.
4. Kawasaki disease.
5. JRA, SLE, dermatomyositis, scleroderma and Behcet disease.

Chapter XVII.1. Neonatal Conjunctivitis and Eye Prophylaxis
Sheree Kuo, MD

This is a 4 week old male infant born to a 26 year old G2P2 O+, rubella immune, group B strep negative, HBsAg negative, VDRL negative, GC and Chlamydia negative married female at 40 weeks gestation via spontaneous vaginal delivery with Apgar scores of 8 and 9 at 1 and 5 minutes. Pregnancy, delivery and postpartum hospital course were uncomplicated. He presents with his mother to your office with a two day history of bilateral eye drainage. He had been in good health until two days ago when he developed yellow drainage and mild periorbital swelling. Review of systems is negative except for the recent development of a cough that he "probably caught from his older brother".

Exam: VS T37.5, P 120, RR 60, BP 60/40, oxygen saturation 94% in room air, weight 4.0 kg (50%ile) He is a well developed, well nourished, non-toxic male infant with mild tachypnea and staccato cough, but in no acute distress. His upper and lower eyelids are edematous. There is mild conjunctival injection with moderate amounts of mucopurulent drainage bilaterally. Pseudomembranes are seen with eversion of the upper eyelids. Coarse breath sounds are appreciated bilaterally with occasional rales and fine expiratory wheezes. The remainder of his exam is unremarkable.

You swab the conjunctiva for gram stain, culture and chlamydia direct fluorescence antibody staining. Complete blood count is remarkable for eosinophilia. Chest radiograph reveals bilateral patchy infiltrates with hyperinflation. After receiving positive chlamydia DFA results, you inform the mother of the diagnosis. Initially shocked, she admits that six months ago she and her husband had separated briefly, but are now back together.

Ophthalmia neonatorum is the most common ocular disease in the newborn, occurring in 2-12% of neonates (includes chemical conjunctivitis). The major causative agents of neonatal conjunctivitis are chemical, chlamydial and bacterial. Viral ocular infection, usually by herpes simplex virus, occurs infrequently. The mode of infectious transmission is believed to be acquisition during passage through a colonized or infected birth canal (1,2). While nearly every bacterial species has been implicated, ocular infection with Neisseria gonorrhoeae is felt to be one of the most serious because of its potential to damage vision and cause blindness (1,3).

Gonococcal ophthalmia prompted the widespread use of silver nitrate for prophylaxis in the neonate since the 1880's. Consequently, Chlamydia trachomatis is now the most common infectious agent causing neonatal conjunctivitis in approximately 0.4%-2.8% births in this country (4,5). Recognizing the irritant effects of silver nitrate (frequently causes chemical conjunctivitis), 0.5% erythromycin ointment, 1% tetracycline ointment and 2.5% povidone-iodine solution have all been suggested and utilized as less chemically irritating alternatives in preventing neonatal gonococcal conjunctivitis. However, none have been shown to consistently prevent chlamydial conjunctivitis or nasopharyngeal colonization (1-4,6-9).

The presentation of ophthalmia neonatorum varies with the causative agent. Inflammation due to chemical irritation (usually silver nitrate drops) is first appreciated 6-12 hours after birth with spontaneous resolution by 24-48 hours. In contrast, the incubation period for N. gonorrhoeae is 2-5 days (sometimes longer) with the appearance of symptoms seen from birth to beyond 5 days of age. Beginning with a mild inflammation and serosanguineous drainage, gonococcal ophthalmia soon results in thick, profuse purulent discharge and tense eyelid edema with marked chemosis (swelling of the conjunctiva) (2,10).

Chlamydial conjunctivitis in the neonate can present from 3 days to beyond 6 weeks postnatal age, but most commonly occurs during the 2nd week of life. Infants present with conjunctival inflammation, mucopurulent discharge (that may be profuse), eyelid edema and pseudomembranes in the palpebral conjunctiva (5,10).

A distinct pneumonia occurs in 10-20% of infants exposed to C. trachomatis (2,5). Patients typically present with a history of afebrile illness for several weeks. The infant usually appears well with tachypnea and prominent "staccato" cough. Auscultation of the chest often reveals rales and wheezing. Fifty percent of these patients also have concomitant conjunctivitis. Chest radiograph reveals bilateral, diffuse, patchy infiltrates and hyperinflation. CBC commonly reveals moderate eosinophilia (5).

The list of causative agents of ophthalmia neonatorum includes, but is not limited to, chemical irritants, Neisseria gonorrhoeae, Chlamydia trachomatis, Staphylococcus aureus, group A or B streptococcus, S. pneumonia, Haemophilus influenzae, Pseudomonas aeruginosa and Herpes simplex virus (1,2).

Shortly after birth, ophthalmic prophylaxis for gonorrhea should be administered to all infants, including those delivered by cesarean section since ascending infection can occur. Two drops of a 1% silver nitrate solution or a 1 cm ribbon of antibiotic ointment (0.5% erythromycin or 1 % tetracycline) are applied to each lower conjunctival sac. The eyes should not be flushed or irrigated (8). Currently, there is no antibiotic agent effective for use as prophylaxis for Chlamydia ophthalmia neonatorum (1-4,6-9). Chemical conjunctivitis is self-limiting and requires no treatment.

Diagnosis of ocular infection with N. gonorrhoeae can be made following identification of gram negative oxidase positive diplococci on gram stain or culture of conjunctival swabbings or eye drainage. Cultures of blood, CSF, or other sites of infection should be obtained in infants with gonococcal ocular infection to rule out disseminated infection. Tests for concomitant C. trachomatis, T. pallidum, and HIV infection should also be performed. For nondisseminated N. gonorrhoeae ophthalmia neonatorum, infants should receive ceftriaxone (25-50 mg/kg IV or IM) once. Alternatively, 100 mg/kg of cefotaxime (IV or IM) can also be given. Therapy is extended to 7 days for septicemia and 10-14 days for meningitis. Frequent saline irrigation of the eyes should also be performed until the discharge is eliminated. Infants born to mothers with untreated gonococcal infection should receive a one-time dose of IM or IV ceftriaxone or cefotaxime (9).

Chlamydia can be detected by PCR, ligase chain reaction (LCR), DNA probe, direct fluorescent antibody (DFA) tests, enzyme immunoassays (EIAs), or by isolating the organism in tissue culture. Diagnosis of chlamydial infection should prompt testing for other STDs in the infant as well as examination of the mother and her sexual partners. Infants who develop chlamydial conjunctivitis with or without pneumonia should be treated with oral erythromycin (50mg/kg/day in 4 divided doses) for 14 days. Treatment with topical antibiotics will not eliminate nasopharyngeal colonization and conjunctivitis may recur (5). In cases where the infant is less than 6 weeks of age, parents should be counseled regarding a reported association between oral erythromycin and infantile hypertrophic pyloric stenosis. Retesting for C. trachomatis is not indicated once treatment has been completed unless symptoms persist (3).

Without prompt treatment, N. gonorrhoeae ocular infection may spread to the deeper layers of the conjunctiva and cornea (2,10). Corneal ulceration and perforation, iridocyclitis, anterior synechiae, and panophthalmitis from untreated gonococcal ophthalmitis may result in permanent vision loss and blindness (1,4,6). Disseminated gonococcal disease can result in scalp abscess, bacteremia, arthritis, meningitis or endocarditis (9).

Left untreated, chlamydia conjunctivitis will subside within 2-3 weeks, but chronic infection is common. Chlamydia pneumonia, not conjunctivitis, is the most serious consequence of neonatal C. trachomatis infection (4). The pneumonia is usually mild and deaths attributed to chlamydial pneumonia have not been reported (5). However, the disease can lead to chronic cough and long term pulmonary impairment (4,5).

Questions

1. Which details of this patient's presentation (in the case) distinguish his illness from neonatal N. gonorrhoeae infection?
2. Besides the infant presented in the case vignette, which other family members should be treated for this condition?
3. What etiologies should be considered when a neonate presents with eye drainage?
4. Of 1% silver nitrate solution, 0.5% erythromycin ointment, 1% tetracycline ointment and 2.5% povidone-iodine solution, which is/are considered effective for prophylaxis of ocular chlamydial infection?
5. What is the treatment for C. trachomatis ophthalmia? For N. gonorrhoeae ophthalmia?
6. What are the long-term complications of N. gonorrhoeae ophthalmia neonatorum? Of neonatal C. trachomatis infection?
7. Infants under 6 weeks of age are at increased risk for the development of what disease following treatment with erythromycin?

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Answers to questions

1. Late presentation, presence of pseudomembranes and accompanying pneumonia.
2. The patient's mother and her sexual contacts should seek medical attention and treatment for urogenital chlamydia and other sexually transmitted diseases.
3. Chemical irritants, Neisseria gonorrhoeae, and Chlamydia trachomatis are the most common causes. However, Staphylococcus aureus, group A or B streptococcus, S. pneumonia, Haemophilus influenzae, Pseudomonas aeruginosa and Herpes simplex virus should also be remembered as potential pathogens.
4. None.
5. Infants who develop chlamydial conjunctivitis with or without pneumonia should be treated with oral erythromycin (50mg/kg/day in 4 divided doses) for 14 days. For nondisseminated N. gonorrhoeae ophthalmia neonatorum, infants should receive ceftriaxone (25-50 mg/kg IV or IM) once. Alternatively, 100 mg/kg of cefotaxime (IV or IM) can also be given.
6. Without prompt treatment, N. gonorrhoeae ocular infection may result in corneal ulceration and perforation, iridocyclitis, anterior synechiae, and panophthalmitis leading to permanent vision loss and blindness. Left untreated, chlamydia conjunctivitis will subside within 2-3 weeks, but chronic infection is common. Chlamydia pneumonia is the most serious consequence of neonatal C. trachomatis infection. The pneumonia does not appear to be life threatening; however, the disease can lead to chronic cough and long-term pulmonary impairment
7. Infantile hypertrophic pyloric stenosis.

Chapter XVII.2. Primary Care Eye Examination
Vince K. Yamashiroya, MD

This is a 6 month old baby girl who comes to your office for a well child examination. She has had no problems in the past with her eyes and according to her parents, she tracks well and reaches for objects. Her parents deny any crossing of the eyes when she looks at objects from a distance; however, her mother mentions that she had a lazy eye when she was a child and needed to be operated on.

Exam: Vital signs are normal for age. Her red reflex and corneal light reflex test are normal. Cover test is negative for strabismus. Her extraocular movements appear intact and she is able to follow objects 180 degrees.

You conclude that her eye examination is normal and reassure the mother. You schedule her next appointment when she is 9 months old or earlier if her mother notices a problem.

The examination of the eye is an essential part of an examination since disease or pathology of the eye can result in vision loss. Although there are diseases that are easily noticed, such as conjunctivitis, there are other conditions that are much more subtle. These conditions include leukokoria of retinoblastoma and strabismus that can lead to amblyopia. Without a careful examination of the eyes, these problems can be missed and result in blindness. There are times that patients will come to us because of pain, itchiness, blurriness, redness, or discharge of the eye. As primary care physicians, we should be comfortable with the eye examination to be able to correctly diagnose, treat, or refer our patients for specialty care by an ophthalmologist. This chapter will focus on screening of the eye in the well child since some serious conditions can only be detected early enough through screening.

In order to know how to examine the eye, a basic knowledge of the anatomy of the eye is important. It would be helpful to refer to a diagram of the eye. The eye is made up of three coats. The outer part is the sclera, which is a white shell of the eye, and the cornea. Next comes the uvea, which is made up of the choroid, the ciliary body, and iris. The choroid is a vascular layer between the retina and sclera. The ciliary body, which produces aqueous humor, is on the sides of the lens that focusses the lens. Immediately anterior to the lens is the iris, which is a colored diaphragm that contracts or dilates and regulates the amount of light entering through the lens. And the innermost part is the retina, which contains rods and cones. A part of the retina is the macula, which is minimally vascular and is responsible for the most acute vision. A pit in the middle of the macula is the fovea, which corresponds to the central fixation of vision. Medial to the macula is the optic nerve, which transmits signals from the retina to the brain. There are two chambers, the anterior and posterior chamber, which are divided by the lens. The lens is a media that focusses light. The anterior chamber is between the cornea and the lens, and is filled with the aqueous humor, which is a clear fluid. The posterior chamber contains the vitreous humor, which is a clear jelly filling. The conjunctiva is a mucus membrane that covers the anterior portion of the sclera (bulbar conjunctiva) and the inner part of the eyelids (palpebral conjunctiva).

There are six extraocular muscles that move the eye. They are the superior, inferior, medial, and lateral rectus muscles, and the superior and inferior oblique muscles which are innervated by cranial nerves 3, 4, and 6 (1,2).

The examination of the well child is primarily dependent on his or her age since infants and young children are less cooperative with the examination compared to older children. Also, screening for specific problems is essential at an early age to prevent vision problems later in life.

From birth to 6 months of age, screening tests that can be done are the red reflex, corneal light reflex, and external examination. An infant's eyes are examined from a distance with an ophthalmoscope to look for a red reflex. If the pupillary light reflex (also known as the red reflex) is totally absent in one or both eyes, then corneal opacity, cataracts, retinal detachment, or a large hemorrhage should be suspected. If a pupillary light reflex is present, but it is white (i.e., not red), this is called leukokoria and retinoblastoma should be suspected. Retinoblastoma is often detected by parents when viewing flash photographs of their infant when a white eye reflex is noted while everyone else in the photo has a "red eye". Ideally, the physician should notice this on routine screening before this happens.

Many times, an infant's eyes are closed during the first several days of life. One trick to having them open their eyes is to gently swing them from a vertical to semi-upright position. Turning off the lights would also help dilate the eyes to make the red reflex easier to see.

Another is the corneal light reflex test in which the eyes are viewed with an ophthalmoscope to see if the corneas are symmetrical. The reflection of the light off the cornea should be symmetric. Asymmetry could signify strabismus and warrants a referral to an ophthalmologist.

In doing the external examination, the orbits and globes are examined for symmetry in terms of shape, position, and movement. The eyelids are likewise noted for symmetry and movement. Asymmetry may signify proptosis, cranial nerve palsy, or lid masses (3). Note if the pupils are round and symmetrical. Irregularity could signify an iris coloboma, which is a "keyhole" shaped defect, caused by an embryological defect of closure of the eye. In a child with choanal atresia and ear anomalies, a coloboma (eye defect) can be part of CHARGE syndrome. Corneal size should be assessed since large corneas, together with excessive tearing and photophobia is a sign of infantile glaucoma.

From birth to 3 months of age, healthy infants can appear to have disconjugate or uneven gaze. However, constant jiggling of the eyes, or nystagmus, is abnormal at any age. Scleral or retinal hemorrhages in neonates can occur as part of birth trauma, and will resolve on its own. The color of the sclera should also be noted, since a blue sclera, in addition to multiple bone fractures can signify osteogenesis imperfecta. Also a yellow sclera or icterus can be seen in jaundiced babies. At times, there is mucoid discharge around the medial canthus of the eye, which can be due to nasolacrimal duct obstruction. This problem is corrected by massaging the duct, and most of the time, this will resolved by 1 year of age. However, if it continues past a year, then an ophthalmological referral should be considered for probing and dilation of the nasolacrimal duct.

Visual acuity can be assessed by having the child regard a face or track a brightly colored object. Babies seem to notice faces more than other objects, especially faces that are smiling and showing teeth. At birth, they should be able to focus on a face at about an arm's length away, which is their point of focus (4). At 1 month of age, they can follow to the midline. At 2 months of age, they can follow an object past midline, and at 5-6 months of age, they can follow to 180 degrees (5). It should also be noted that they are very far-sighted at this age.

From 6 months to 4 years of age, in addition to the methods described for the birth to 6 month old, the Cover Test can be used to assess strabismus and vision. This test is done by covering one of the eyes and seeing if the opposite (uncovered) eye shifts, or when uncovered, if the same eye refocusses (this eye shifts away when covered). The best way to do this is to have the child focus on something at a distance (such as a light), and using your thumb as the occluder while holding the head still with your hand so that it does not move.

Before doing the Cover Test, the corneal light reflex can also be done to assess for strabismus, and is less intimidating. The parents or caretakers can be questioned regarding whether they notice one eye being "crooked" when the child looks at something. A note of warning is that "crooked eyes" can be mistaken for pseudostrabismus, especially in a child with epicanthal folds. Pseudostrabismus can be differentiated from true strabismus by the aforementioned tests.

Visual acuity can be assessed by having them follow a face or object, or by testing for optokinetic nystagmus. This is done by having the child look at a slowly rotating drum or cloth with alternating black and white stripes (or colored and white stripes) and noting if the normal nystagmus with this stimulus is present. The two phases of this normal nystagmus are a slow phase when the eyes focus on the target, and a quick, jerky phase when the eyes return to the subsequent target. The drum or cloth should be about an arm's length away. Also, the red reflex should be assessed at this age. Extraocular muscles can be assessed in one of several ways. One is by spinning which is used for infants. What this entails is holding the child up and turning your body several times in one direction, then in the opposite direction, while watching the child's eyes. Another way is to have a child track an object in an imaginary rectangle around his face. Lastly, turning the head quickly will elicit eye movements through vestibular means, although the child will be angry afterwards (4).

From 4 years of age and onward, the eye exam can be performed the same as in adults. Besides looking at the pupils and assessing extraocular movements, funduscopy can be done, and can even be performed in younger children. Although the older child can be cooperative and focus on a stationary object while you view his fundus, in the younger child, funduscopy can be a frustrating experience. One method would be to stay still while viewing the eye, and have the child move his eye for you on his own. When you are about 12 inches away, note if the red reflex is equal in all four quadrants of the fundus. As you get closer, view the optic disk as it passes by. Lastly, look at the bright fovea reflection by telling the child to look at your magic light. Make sure you have the lights off to have maximum pupillary dilatation.

Visual acuity can be assessed by several means, such as having a wall mounted Snellen chart or "E" chart (4). There are also charts available that can be viewed through a desktop instrument. A more technologically advanced tool is Welch Allyn's SureSight Vision screener, which can provide objective data in 5 seconds without any cooperation from the patient; however, it costs about $4,500 in 2002 (6). Keep in mind that an acuity of 20/40 is generally accepted as normal for 3 year olds, 20/30 typical for 4 year old, and 20/20 vision attainable by most 5 to 6 year old children. Referral to an ophthalmologist is indicated if the vision is 20/50 or worse in a 5 year old child, and 20/40 or worse in a 6 year old child (3).

The eye examination is one of the most difficult, yet rewarding experiences in pediatrics. Unfortunately, the only way to become proficient, is to do as many as possible. Remember to do the least intimidating step first (which may be external observation or assessing the red reflex or corneal light reflex), and the most intimidating test last (such as the funduscopic exam). With practice and diligence, the eye examination will become easier and the rewards for discovering preventable pathology that much greater.

Questions

1. What is the differential diagnosis of an absent pupillary light reflex (red reflex)?
2. What condition causes leukocoria?
3. A parent is worried that her Asian baby has crooked eyes. How would you assess whether this is pseudostrabismus?
4. What is the distance of focus for infants?
5. At what age can an infant follow an object to the midline, past the midline, and 180 degrees?
6. How can you assess extraocular movements in the uncooperative or young child?
7. What is one way you can look at the fundus in the uncooperative child?

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Answers to questions

1. Cataracts, retinal detachment, and other pathology that is obscuring the vitreous or aqueous clarity.
2. Retinoblastoma.
3. Performing a Cover Test and corneal light reflex test.
4. About an adult's arm length.
5. To the midline is 1 month, past the midline is 2 months, and 180 degrees is 5-6 months.
6. Two methods are to spin the child and turning his head, both of which use the vestibular systems.
7. By being patient, looking at the child's red reflex in all four quadrants in a stationary position from about 12 inches away, and as you move closer, viewing the optic disk as it passes by, and lastly the fovea by telling the child to look directly at your "magic light."

Chapter XVII.3. Strabismus and Amblyopia

Julie K. Nishimura, MD

A 6 month old female infant presents with crossed eyes. Her parents say her eyes have been crossed since birth, and the left eye seems to cross more than the right. She seems to see fine. She plays with toys and recognizes people across the room. She was a full term infant without perinatal complications, and has no known medical problems.

Exam: She is alert and playful. External: Her left eye is clearly crossed inward (esotropic). There is no facial hemiparesis. Vision: She tracks toys well using both eyes. With the left eye covered, she fixes and follows easily. However, she fusses when the right eye is covered and has more trouble following with this left eye (i.e., she is fussing when the right eye is covered because she can't see as well with her left eye). Motility: Full extraocular movements. There does not seem to be any retraction of the globe on adduction. No nystagmus. Pupils: Equally round and reactive to light; no afferent pupil defect. No leukocoria. Corneal reflection test (Hirschberg test): A penlight is directed toward the cornea, and the reflected image is located temporal to the center of the left pupil. Cover-uncover test: On covering the right eye, there is an outward shift of the left eye. When the eye is uncovered, the left eye shifts back inward. Alternate-cover test: On switching the cover to the left eye, there is an outward shift of the right eye. When the cover is alternated from one eye to the other, there is always an outward shift of the opposite eye.

Clinical course: A referral is made to a pediatric ophthalmologist. No structural ocular abnormalities are found, and there is no significant refractive error. The patient is diagnosed with 1) infantile esotropia and 2) amblyopia, left eye. She wears a patch 6 hours a day over the right eye for a month, and vision in her left eye improves so that she can follow toys equally well with either eye. This also means that either eye crosses spontaneously. She then has surgery to correct her strabismus. Her medial rectus muscles are recessed at age 8 months. Postoperatively, her eyes are straight (orthophoric).

Strabismus (ocular misalignment) is a common pediatric health problem, affecting approximately 5% of U.S. children. If left untreated, strabismus can lead to severe visual consequences, including poor vision and inability to use the eyes together. Strabismic amblyopia is defined as poor vision (usually in one eye, often termed "lazy eye") that results from prolonged ocular misalignment. Amblyopia can be very pronounced (sometimes able to see only hand motions in the affected eye) and is a major cause of blindness among children. Amblyopia can be prevented with timely, appropriate intervention.

There are 2 main forms of strabismus: esotropia and exotropia. Esotropia is an inward deviation of the eyes, and exotropia is an outward deviation. Less common forms include hypertropia (upward deviation) and hypotropia (downward deviation).

Infantile esotropia is the most common type of infantile strabismus. It is defined as an esotropia present by 6 months of age. Previously it was termed congenital esotropia, but many no longer use this term as it is often not noted from birth. There can be a family history of strabismus. Children with infantile esotropia are usually otherwise healthy, although a higher incidence is noted with cerebral palsy and hydrocephalus.

The deviation is usually large, with a definite "crossed-eyes" appearance. The vision can actually be equal in both eyes, but up to 40% will have associated amblyopia. It is actually a good sign if the eyes alternate crossing inward, because this often indicates that vision is approximately equal between the two eyes.

An estimate of the amount of esodeviation can be made with corneal reflection testing. The Hirschberg estimate involves shining a light onto the cornea. If an eye is deviated inward, the light reflex will be temporal to the pupil center.

The definitive method of testing for strabismus is the cover-uncover test. An occluder is placed over the fixing eye. The opposite eye is observed. If there is a deviation of the opposite eye, a tropia is present. If the opposite eye shifts outward, an esotropia is present. If the opposite eye shifts inward, an exotropia is present.

There are a few other entities in the differential diagnosis of infantile esotropia. Pseudoesotropia (pseudostrabismus) is the most common, where a wide, flat nasal bridge with prominent epicanthal folds gives a crossed appearance. Accommodative esotropia is also frequent, where the patient is far-sighted (hyperopic) and the strain to focus causes the eyes to turn inward. This usually occurs in patients older than 6 months of age and is treated with glasses. Sixth-nerve palsy should be ruled out by checking for abduction in both eyes. Sensory deprivation esotropia is caused by unilateral vision-limiting lesions, such as retinoblastoma or cataract. Nystagmus-blockage syndrome features nystagmus dampened by convergence, leading to esotropia. Rarer entities are Duane syndrome (agenesis of the sixth nerve nucleus, accompanied by globe retraction on adduction) and Mobius syndrome (palsy of sixth, seventh, and twelfth cranial nerves).

Treatment of infantile esotropia begins with addressing amblyopia, if present. The stronger eye is patched several hours each day, to develop vision in the weaker eye. Once the vision seems approximately equal, chances for success with surgery are greater. Surgical alignment is usually done with bilateral medial rectus recessions. This procedure involves detaching the medial rectus muscles from their scleral insertion sites, then suturing them to the sclera several millimeters behind the original insertion sites. This effectively weakens the muscles, diminishing their adducting effect. Surgical alignment has traditionally been recommended by two years of age, but more recent studies have supported alignment by one year of age. Earlier surgery provides better levels of stereoscopic depth perception (called stereopsis).

Children need to continue to have close follow-up after surgery, to monitor for postoperative misalignment or amblyopia. They can become overcorrected (exotropia) or have residual esotropia. They sometimes require further surgery for recurrent misalignment and other motility disorders. Alignment to near-orthophoria is the typical goal. This results in a stable alignment with an excellent appearance.

Questions

1. What is the most common form of infantile strabismus?
2. What is the upper age limit in the definition of infantile esotropia?
3. How is amblyopia most commonly treated?
4. Name 3 entities in the differential diagnosis of infantile esotropia.
5. By what age should surgery be undertaken for infantile esotropia?
6. What is the consequence of not recognizing infantile strabismus in a timely fashion?

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Answers to questions

1. Infantile esotropia.
2. 6 months.
3. Patching.
4. Possible answers: pseudoesotropia, accommodative esotropia, sixth nerve palsy, sensory deprivation esotropia, nystagmus-blockage syndrome, Duane syndrome, Mobius syndrome.
5. 1 year of age.
6. The child will have a permanent reduction in visual function. This can range from reduction of stereopsis to total blindness in one eye. It is possible for stereopsis to be lost even if visual acuity is preserved (i.e., measured visual acuity is 20/20) since stereopsis is dependent on vision, plus integration and processing of the images by the brain.

Chapter XVII.4. Eye Infections and Conjunctivitis

Peggy M. Liao, MD

A 28 month old female presents to the pediatrician with a swollen right upper eyelid for one day. Her mother says that the eyelid had a small red lump 2 days prior, but the eyelid became progressively swollen. The patient has a low grade fever, but she is otherwise still playful. The pediatrician diagnoses that the patient has right upper eyelid cellulitis and prescribes oral antibiotics and warm compresses. After 2 days of antibiotics, the eyelid is still swollen and red. The patient is admitted to the hospital for intravenous antibiotics and within 48 hours, and eyelid is less swollen and the patient is discharged for a total of 14 days of systemic antibiotics.

Preseptal eyelid cellulitis (periorbital cellulitis) is an infection confined to the tissues anterior to the orbital septum. External trauma, such as cuts and insect bites, as well as internal inflammation, such as hordeolum and dacryocystitis can cause eyelid cellulitis. Symptoms include tenderness, swelling and redness of the involved eyelid. Young children may also present with fever. Signs include edema, erythema, warmth and pain of the eyelid. Visual acuity, eye motility, and pupillary reaction are normal. The conjunctiva can be injected, and there should be very little pain on eye movement.

Teenagers and adults can be treated with oral antibiotics, and followed as outpatients. Preseptal cellulitis in infants and children caused by Haemophilus influenzae type B, can spread to septicemia and meningitis, therefore all febrile children with preseptal cellulitis were hospitalized in the past and treated with IV antibiotics. However, since widespread Haemophilus influenzae type B vaccine has virtually eliminated this pathogen, cellulitis with group A strep and Staph aureus are less likely to cause septicemia, thus, they can usually be treated as outpatients with clindamycin. Cultures from conjunctiva and blood can be obtained, but the yield is not high. Conjunctival cultures do not necessarily reflect the etiology of the cellulitis and blood cultures are only positive in bacteremic or septic patients. CSF should be obtained via a lumbar puncture if meningitis is suspected. Diagnostic imaging may be necessary if the patient does not respond to treatment or a subcutaneous abscess is suspected. Antibiotic selection is based on history and examination, but staphylococcus aureus and streptococcus are the most common organisms in patients with eyelid cellulitis caused by trauma.

When the orbital structures posterior to the orbital septum are infected, it implies orbital cellulitis (as opposed to periorbital cellulitis). Signs include proptosis, restricted ocular motility (or pain with eye movement), decrease in visual acuity and sometimes, abnormal pupillary reaction. CT scan is mandatory in these patients to detect possible subperiosteal abscesses. Diagnostic imaging also helps in detecting infections extending from periorbital sites which are not uncommon. They include paranasal sinuses, dental infections and trauma with retained orbital foreign bodies. Draining of abscesses may be necessary for the patient to improve. Otolaryngology consultation should be sought if sinusitis is present to consider draining the sinuses as well.

A chalazion is a granulomatous mass results from an obstruction of the meibomian gland. Meibomian glands are oil-producing glands with openings just posterior to the eyelash line (the tarsal margin). When the openings of the glands are plugged, the sebum is released into the surrounding tissue, inciting an inflammatory response with pain, erythema and a mass. They are not considered infectious, unless eyelid cellulitis ensues. The main treatment includes warm compresses, topical and/or systemic antibiotics, topical anti-inflammatory medications and eyelid hygiene. The term "hordeolum" usually refers to the acute phase of a chalazion.

The conjunctiva is a thin layer of non-keratinized mucous membrane which covers the surface of the eyeball (bulbar conjunctiva) and inner layers of the eyelids (tarsal or palpebral conjunctiva). Conjunctivitis describes inflammation of the conjunctiva and is a nonspecific entity. It is easiest to classify conjunctivitis into infectious versus non-infectious.

Infectious conjunctivitis can be further sub-classified into etiologies, such as viral, bacterial, chlamydial (or trachoma), and others. Non-infectious conjunctivitis can include allergic, chemical, or toxic conjunctivitis.

Watery and thin mucus discharge accompanied by red and swollen eyelids are signs of viral conjunctivitis, usually caused by adenovirus. Onset can be acute, and bilateral involvement is usual, but one eye can be involved first. Preauricular adenopathy is common, along with conjunctival membranes or pseudomembranes. Patients may have URI symptoms prior to the onset of the conjunctivitis. Treatment is supportive, with cool compresses and artificial tears. Conjunctivitis may take up to 21 days to resolve. Viral conjunctivitis is very contagious, especially for the first few days. Patients should be told to wash their hands, avoid touching their eyes, sharing towel,

bedsheets or pillow cases. Similarly, other household members should wash their hands frequently and avoid touching their eyes to reduce their likelihood of acquiring the infection from the household. Children should stay away from school for at least the first 3 to 7 days.

Herpes simplex can cause conjunctivitis indistinguishable from other viral conjunctivitis, but herpetic skin vesicles along the eyelids should raise the suspicion. Topical antiviral therapy and sometimes systemic antiviral therapy are recommended.

Purulent discharge is an important sign of bacterial conjunctivitis. If the onset is hyperacute, i.e., within 12 hours, a smear should be taken from the eye to rule out gonococcal conjunctivitis. Otherwise, a routine culture should be taken and a topical broad-spectrum antibiotic, such as erythromycin ointment or sulfacetamide drops can be used for 5 to 7 days.

Chlamydial inclusion conjunctivitis is a sexually transmitted infection, typically occurring in teenagers and young adults. It is usually chronic with typical tarsal conjunctival follicles. A definitive diagnosis can be made by direct chlamydial immunofluorescent test and or chlamydial culture. Both the patient and the sexual partners must be treated with oral erythromycin or doxycycline for 3 weeks.

Trachoma can present in a similar fashion to chlamydial conjunctivitis, but this principally occurs in immigrants from underprivileged countries. Trachoma (due to chlamydia trachomatis) is the leading cause of acquired blindness in many countries, but it is rare in the U.S. Trachoma is classically acquired by workers in rug factories where the occupational risk of poor air quality (dust and rug fibers presumably) places the factory workers at risk for trachoma.

Allergic conjunctivitis is the most common non-infectious conjunctivitis. Itching, watery discharge, chronicity, red eyes and a history of allergies are typical symptoms. Some allergic conjunctivitis are seasonal, but others can be year-long. If the inciting agent can be identified, such as cat fur and animal dander, it should be eliminated. Cool compresses help decrease itchiness, and are preferable to rubbing the eyes. Over-the-counter artificial tears and vasoconstrictor drops (naphazoline/pheniramine) can be used for mild cases.

Topical mast-cell stabilizers (cromolyn, Alomide) work well as preventive measures if the patient's allergies are seasonal. Topical antihistamines have a faster onset of action. In severe cases, topical corticosteroids may be needed, but patients must be monitored for side effects associated with prolonged topical steroid use, such as cataracts, and glaucoma. Concomitant oral antihistamines are helpful if the patient has systemic allergies.

Acute allergic conjunctivitis frequently presents with impressive edema of the conjunctiva. The conjunctiva can become so edematous that it lifts off the sclera and frequently protrudes out. The pale, watery edema resembles a lychee fruit (without the skin). Topical vasoconstrictors and antihistamines are used to treat this.

When an eye is exposed to acidic or basic chemicals, copious irrigation with water or normal saline should be started as soon as possible. Litmus paper can be used to test the tears for neutrality. If the cornea has been burned with the chemical, an ophthalmology consult needs to be obtained. Otherwise, the conjunctivitis can be treated with frequent artificial tears and moisturizing eye ointments.

Occasionally, prolonged exposure to topical eye medications can cause conjunctivitis, especially the aminoglycosides, such as gentamicin and tobramycin, and certain glaucoma medications. Additionally, patients may have allergic reactions to other topical antibiotics such as sulfonamides.

Questions

1. Herpes simplex conjunctivitis:
   a. may be chronic.
   b. may be associated with skin vesicles.
   c. may recur.
   d. all of the above.

2. Common causes of periorbital cellulitis include the following:
   a. sinusitis
   b. chalazion
   c. dental infection
   d. eyelid skin laceration

3. A three-year old boy presents with an acute red lump in his right upper eyelid, the pediatrician diagnoses that it is an acute chalazion. What are the proper treatments?
   a. warm compress
   b. antibiotic eyedrops
   c. oral antibiotics
   d. topical corticosteroid

4. An 18 year old female presents with a chronic follicular conjunctivitis and a diagnosis of chlamydial conjunctivitis is made. What is the proper treatment?

5. A four month old male has congenital tear duct obstructions and has symptoms of chronic tearing and mucus. His primary care physician prescribes topical sulfacetamide drops three times a day to clear up the mucus, but after using the drops for one month, his eyelids are more erythematous than ever and the conjunctiva is more swollen and he constantly rubs his eyes. What should be done?

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Answers to questions

1. The answer is d. Herpes simplex conjunctivitis can present with all of the above.

2. The answer is all of the above. Although a skin laceration is easily diagnosed, a sinusitis needs to be confirmed with a CT scan. A chalazion is usually diagnosed by history or a fluctuant skin mass in the eyelid. A dental infection involving the upper teeth can easily spread itself into the orbit.

3. Topical corticosteroid is the only choice that is not appropriate for a primary care physician to prescribe. The rest of the choices are appropriate, although most chalazia do not require oral antibiotics.

4. Topical erythromycin for two weeks and oral erythromycin for two weeks for the patient AND oral erythromycin for two weeks for her sexual partner.

5. The baby is probably developing an allergic reaction to the long-term use of topical sulfacetamide. The eyedrops should be discontinued right away and patient can be treated with tear duct massage and another antibiotic eyedrop on an as-needed basis.

Chapter XVII.5. Corneal Abrasions
Peggy M. Liao, MD

An 8 year old boy presents to the emergency department with moderately severe left eye pain 6 hours after riding his bicycle through some low hanging leaves from a tree. He didn't notice the tree branches until a few leaves hit him in the face. He has no bleeding wounds.

Exam: VS are normal. He does not want to open his left eye because of discomfort. Some anesthetic eye drops are instilled into his left eye. He complains that this burns a lot and he begins to cry. After 10 minutes (topical anesthetic usually works within minutes), he is able to open his eye. His visual acuity was 20/20 in the right eye and 20/30 in the left eye. His pupils are equal and reactive. His conjunctiva is slightly injected. No hyphema is visible. A drop of saline is placed on a fluorescein paper strip. This drop is then touched to his lower eyelid so fluorescein dye flows over the surface of his eye. With an ultraviolet light, a 0.5 cm linear abrasion is seen in the lateral aspect of his left cornea.

His eye is rinsed with saline to remove excess fluorescein. A single drop of a cycloplegic agent (such as homatropine) is instilled into his left eye. Antibiotic ointment is instilled into his eye and a pressure eye patch is applied. He is instructed to take over-the-counter analgesics for pain.

The next day he is checked by his primary care physician. The fluorescein exam is repeated and no corneal abrasion is seen. No further treatment is necessary.

The cornea is composed of three layers: the outer epithelium, the middle stroma and the inner endothelium. The outer epithelium is the only layer capable of regenerating. Injuries to the stroma and endothelium usually result in permanent scarring of the cornea, and reduced vision for the eye. Cornea has a high density of neuronal pain receptors, making injury to the cornea very painful.

Epithelial damage is commonly called corneal abrasion. The most common cause is external blunt trauma, such as foreign objects scratching the cornea. Other causes include chemical burn, thermal burn (such as welding and sun lamps), or prolonged exposure to ambient environment, such as decreased blinking and dry eyes, and contact lens wear. Occasionally, there is no history of trauma. Symptoms of corneal abrasion include pain, redness, photophobia, tearing, and foreign body sensation. Signs of corneal abrasion include conjunctival injection, or redness, swollen eyelid, and sensitivity to light. Occasionally, a visible irregularity of the corneal surface can be seen.

It is very important to document visual acuity when examining a patient with an eye injury. A topical anesthetic, such as proparacaine or tetracaine, can be instilled to decrease pain for the patient to facilitate the examination. Visual acuity should then be obtained and documented. Take note of any periorbital injuries, such as eyelid trauma, or possible orbital wall fractures. These separate injuries should be treated appropriately as well.

Ideally, an eye should be examined with a slit lamp for signs of corneal abrasion. Fluorescein is applied topically, and using cobalt blue light, the size, shape and location of the abrasion should be documented. Slit lamp examination is also helpful in determining if the injury involves deeper layers of the cornea, and possibly penetrating injury to the eyeball. Despite this advantage, most non-ophthalmologists use a plain ultraviolet light (Wood's lamp) with fluorescein to examine the cornea for abrasions. Eyelids are everted to look for foreign bodies.

The traditional treatment for corneal abrasion involves "pressure patching" the eye after topical cycloplegic and antibiotic drops or ointment are applied. The cycloplegic reduces the pain due to ciliary muscle spasm and the topical antibiotics provide prophylaxis against infection developing in the abrasion. A gauze eye patch is folded in half and placed over a closed eye. A second gauze eye patch is applied over the first eye patch, making sure the eye is completely closed. Paper tape is applied tightly over the patches from the forehead to the cheek. This type of treatment ensures that the epithelium can regenerate without having the eyelid abrading further on the corneal abrasion. Narcotic analgesics are sometimes necessary to treat the pain. The patches are left on 24 hours at a time, and the eye is reexamined for progress. Most corneal abrasions heal in 24 to 72 hours. If infiltrates are observed at any time, patching is discontinued and the patient needs to be treated for a corneal ulcer by an ophthalmologist.

A pressure patch is not recommended for abrasions which are at significant risk for infection, such as scratches from a tree branch, from a dirty fingernail, and abrasions in a contact lens wearer. These eyes are treated with every 1 to 2 hour applications of topical antibiotic ointment, until the abrasions heal completely. Eye patches are not always necessary and it is not possible to keep these on some young children.

Excessive ultraviolet light exposure to the cornea (and retina as well) can occur when observing a welding arc or flame, or with extremely bright sunlight exposure such as looking at the sun, during high altitude skiing (commonly called snow blindness), and occasionally at the beach. The welding arc produces invisible high intensity ultraviolet radiation which must be blocked by an ultraviolet light shield. Just as in a sunburn, patients with ultraviolet corneal burns do not notice much discomfort initially, but after 1 to 2 hours have passed, the burning sensation becomes very painful. Fluorescein examination reveals multiple, tiny pitting defects of the corneal surface, called superficial punctate keratopathy. Since this is usually a bilateral problem, bilateral eye patching is not usually feasible. Frequent topical antibiotic ointment is recommended and oral narcotic analgesics may be necessary for comfort. If only confined to the cornea, and not involving the retina, this problem is generally self limited.

A hyphema is defined as blood in the anterior chamber of the eye. It is usually caused by blunt trauma. The eye ball is compressed and it results in distortion of the iris and angle, thus causing tears in the iris and the angle vessels. It can present as a microhyphema,

where only circulating red blood cells are present, or as a visible blood clot. The blood is generally reabsorbed by the trabecular meshwork over time. The greatest danger of hyphema is re-bleeding, which usually occurs between the 2nd and the 5th day after the initial injury. Re-bleeding is probably caused by clot retraction and fibrinolysis. Re-bleeds are associated with an increased incidence of glaucoma and decreased final visual acuity.

The management of hyphema remains controversial, but most experts agree that children should be placed on bed rest with bathroom privileges for at least 5 days and refrain from strenuous activities for 10 days. A fox shield (a metal shield) is also recommended to decrease the chance of further blunt injury in the early days. Topical corticosteroids, oral corticosteroid, and aminocaproic acid (anti-fibrinolytic agent) have all be advocated to decrease the incidence of re-bleeds. Occasionally, surgical evacuation of a blood clot is necessary to decrease complications, such as uncontrollable intraocular pressure, and corneal blood staining (permanent opacification of the cornea from infiltration of hemoglobin and hemosiderin).

Questions

1. An eye with a corneal abrasion should be patched if:
    a. it is associated with a corneal infiltrate.
    b. it has been scratched by a fingernail.
    c. it occurs in a contact-lens wearer.
    d. it is large and is in the center of the cornea.

2. A 4 year old boy was playing with sparklers on the 4th of July. He held it up high and his parents think that some sparks fell into his eye. He has some small blisters around his eyelids and he is complaining of intense eye pain. He refuses to open his eyes for an examination because of pain. Which of the following are possible options (more than one correct answer is possible):
    a. topical proparacaine as a single dose to facilitate an examination.
    b. intramuscular morphine to facilitate an examination.
    c. topical proparacaine now and p.r.n. at home for discomfort.
    d. acetaminophen with codeine syrup.

3. A 10 year old boy presents to the pediatrician with a red and teary eye for a day. He had been to a soccer practice on the day before presentation and the red eye began after that. The pediatrician does not see a corneal abrasion with fluorescein and sends him home with topical antibiotics. He still has the same symptoms the next day. What should the pediatrician do?

4. A 16 year old female presents to the primary care doctor with the complaint of bilateral red and painful eyes since waking up. She had forgotten to take off her soft contact lenses the night before because she was too tired. The primary care physician does not see any corneal abrasions but there are some small "white" dots in the corneas. What should be done?

5. A 4 year old boy presents to the emergency room with a red and painful right eye after a swing had accidentally hit the eye on the playground. On examination, he does not like to have the left eye covered because he "cannot see". The eyelids are swollen and ecchymotic and the conjunctiva has hemorrhages. The physician sees a blood clot covering 65 percent of the anterior chamber. What is the appropriate management?

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Answers to questions

1. Choice d is the correct answer. A corneal abrasion which is at significant risk for infection should not be patched. Choices a, b, and c are all at higher risk for infection.

2. Choices a and b are all reasonable answers. Choice d would be too slow for an office or emergency department, but it would be reasonable if one is willing to wait for it to take effect. Choice c is incorrect because topical ophthalmic agents should not be sent home with patients. Prolonged corneal anesthetic use often results in corneal complications because this blocks the eye's natural protection reflexes to minimize further corneal injury.

3. The differential diagnosis consists of corneal foreign body, conjunctival foreign body, early conjunctivitis. The eyelids should be flipped to look for small foreign bodies. If possible, the cornea should be inspected again with some magnifying glasses to look for a foreign body as well.

4. Whenever the cornea has white lesions, one should always suspect corneal ulcers or infiltrates. Overnight contact lens wear is the most significant contributor to the development of corneal ulcers in a contact lens wearer. The patient should be referred to an ophthalmologist as soon as possible and the patient should be advised to discontinue contact lens wear until treatment is completed.

5. The patient should have an ophthalmology consult as soon as possible. A metal shield should be placed on the eye, NOT a gauze eye patch (which can press on the eyeball), to decrease further chance of injuring the eye. He probably should be admitted to the hospital for bedrest and observation to decrease the chance of re-bleed.

Chapter XVIII.1. Neurologic Examination
Vince K. Yamashiroya, MD

A mother brings her 4 year old son into your office for headaches occurring for the past month which are getting worse. In the beginning, he would complain of headaches during the daytime but these would resolve after several hours and he would run out and play. During the past several days, he has been complaining of worsening headache, sometimes waking him from sleep in the early morning, occurring almost every day. These recent headaches have been associated with vomiting and he has been clumsier on the playground. There has been no history of trauma, fever, respiratory symptoms, or visual problems.

PMH is unremarkable. His growth and development have been normal.

Family history is significant for migraines in his mother and other relatives.

Exam: VS T 37.0, P 80, R 20, BP 120/80, Weight 17 kg, Height 105 cm, HC 50 cm (all in the 50th percentile). He is a healthy appearing, alert boy in no distress. No unusual odors are present. No rashes or neurocutaneous stigmata are visible. His head is normocephalic and atraumatic. No dysmorphic features are seen. TMs are clear. Throat is normal. Lungs, heart, and abdomen are all normal. There are no sacral dimples on his back.

Neurologic exam: Pupils are equal and reactive to light. Extraocular movement is impaired on lateral gazing of the left eye. The rest of his EOMs are intact. Horizontal nystagmus is exaggerated towards the left, no vertical or rotatory nystagmus is present. Funduscopic examination reveals papilledema without retinal hemorrhages. Visual acuity is 20/20 for both eyes. No facial asymmetry noted when smiling or closing his eyes. Hearing tested with tuning fork is equal on both sides. His gag reflex is intact. He is able to shrug his shoulders and turn his head in both directions. His tongue is midline. His biceps, triceps, deltoids, knee flexors and extensors strength are 5+/5. He is not able to do finger to nose testing. Dysdiadochokinesia is present. He has a stumbling gait. His temperature sensation is intact. He is able to discriminate coins, paper clips, and rubber bands. His deep tendon reflexes are +2/4. No clonus present. He has a negative Babinski.

The history is significant for signs of increased intracranial pressure with headache and vomiting. You wonder about cerebellar dysfunction because of his clumsiness. The physical examination confirms this with papilledema and cerebellar signs with dysdiadochokinesia. You determine that the lesion probably originates from the cerebellum and may be on the left side because of the left eye paresis on lateral gaze and exaggerated horizontal nystagmus to the left. Putting all of this information together, especially remembering that four year olds normally do not complain of headaches and the additional fact that the headaches are severe enough to wake him at night, makes you suspect that this child has a tumor in his cerebellum. An MRI of his brain demonstrates acute hydrocephalus and a cerebellar astrocytoma.

Physicians are often thought of as detectives since it is their goal to determine where any lesion or problem is. They have to be systematic in their approach in order not to miss anything. By careful history taking and physical examination, they try to determine where the problem is, and only then do they obtain further diagnostic studies to confirm or localize the area of involvement. The pediatric neurologic examination is often challenging to those who have primarily worked with adults since infants and younger children are often uncooperative. This chapter will focus on two major areas of the examination, the history and physical examination.

History. A careful and accurate neurologic history is the most important part of the assessment. In evaluating the history of present illness, it is important to note the onset of symptoms in chronological order, and their frequency, duration, and associated characteristics (1). Also, it would be useful to know whether the problem is static, progressing, or improving. Children who are older than 3 to 5 years may be able to give answers to questions if done appropriately, which may not only be helpful but could be more accurate than the parent's. The review of symptoms is also important since vomiting, fever, clumsiness, and other symptoms can be associated with the presenting problem. A birth history should be obtained, focusing on prenatal, perinatal, and postnatal events. Ask about the gestational age, complications during pregnancy (including infections), maternal drug and alcohol use, Apgar scores, problems during delivery - like meconium, and feeding difficulties. The past medical history should include immunization status, accidents, chronic medical problems, and medications (including anticonvulsants). A good developmental screening assessment with milestones can be performed (such as the Denver II). Family history can also be useful since some diseases are transmitted through dominant genes like some neurocutaneous syndromes and migraines, or through recessive genes such as the case of many neurodegenerative disorders (2).

General Physical Examination. The following is a list of items that should be performed in the general examination (2).

1. Height, weight, blood pressure, and head circumference. For neonates, nurseries commonly include the chest circumference. If the head circumference is significantly smaller than the chest circumference, then there might be microcephaly. A nice rule of thumb for head circumference is the 3 & 9 rule. A newborn has a head circumference of 35 cm, a 3 month has a circumference of 40 cm, a 9 month has a circumference of 45 cm, a 3 year old has a circumference of 50 cm, and a 9 year old has a circumference of 55 cm (3).
2. General appearance, including dysmorphology.
3. Skin examination for neurocutaneous lesions, such as ash leaf spots, cafe au lait spots, angiomas, axillary freckling, adenoma sebaceum, or shagreen patches.
4. Location of the hair whorl and appearance of palmar creases. Abnormal hair whorl location can signify the presence of cerebral malformations.
5. Quality of scalp hair, eyebrows, and nails. Friable, kinky hair may signify Menkes kinky hair disease that is associated with mental retardation and optic atrophy.
6. Examination of the midline of the back and neck for sacral dimples, tufts of hair, or other signs of spinal dysraphism.
7. Comparison of thumbnail sizes and their convexity. Abnormalities may signify a growth disturbance, which may be a sign of hemiparesis.
8. Presence of unusual body odor, which is present in some inborn errors of metabolism.

Neurologic Examination of the Child. The process is the same as that of the adult, although one must remember that children are often frightened of those with white coats and their attention span is rather short. Therefore, the following general tips should be kept in mind:

1. Use items such as a tennis ball, small toys (including a toy car), bell, and an object that will attract the child's attention (like a pinwheel).
2. Do not wear a white coat.

3. Postpone uncomfortable tasks until the end, such as funduscopy, corneal and gag reflexes, and sensory testing.

4. Make the most of every opportunity to examine the child. See how he or she plays, taking into account handedness and motor deficits.

5. Examine the younger child in the parent's lap. Be patient and wait for the child the make the first move before touching him or her. Give the child a toy to establish rapport.

The examination can be summarized in the following steps: 1) Examination of the skull. 2) Cranial nerves. 3) Strength. 4) Cerebellar function. 5) Sensory. 6) Reflexes.

The examination of the skull can lead to the discovery of microcephaly, macrocephaly, and craniosynostosis (or premature closure of the cranial sutures). Prominence of scalp veins may signify increased intracranial pressure. Flattening of the occiput is seen in children who are developmentally delayed, while prominence of the occiput may signify Dandy-Walker syndrome. Ridging of the cranial sutures is a sign of craniosynostosis. Percussion of the skull showing areas of tenderness may signify osteomyelitis. Macewen (cracked pot) sign is where the sutures are separated, which may indicate increased intracranial pressure. Palpation of the anterior fontanelle is also important since one can estimate intracranial pressure. If the anterior fontanelle is bulging, then increased intracranial pressure may be present. The skull can be auscultated using the bell of the stethoscope in six locations for bruits: globes, the temporal fossae, and retroauricular or mastoid areas. Intracranial bruits are heard in many cases of angiomas, which are often accompanied by a palpable thrill. They can also be heard in anemia, thyrotoxicosis, and meningitis (2).

Cranial nerves (2). CN I (olfactory) is rarely tested although it can be by asking the patient to smell something. Olfactory sensation appears at 5 to 7 months of age. CN II (optic) can be tested through various means. Funduscopic examination can be performed, and appearance of the optic disk, macula, and retina noted. An early sign of papilledema is obliteration of the disk margins and absent pulsations of the central veins. Visual acuity can be tested by a vision chart or by offering toys of various sizes to the younger, uncooperative child. Rotating a striped drum or drawing a strip of cloth with black and white squares in front of the eyes can test for optokinetic nystagmus. A homemade drum can be made by attaching a paper with alternating black and white stripes around an empty soda can with a metal wire piercing through it (4). Alternatively, optokinetic nystagmus can be elicited by passing a vertically striped cloth horizontally across the patient's visual field. Optokinetic nystagmus can be elicited starting about 4 to 6 months of age and it confirms cortical vision, in addition to supporting the integrity of the frontal and parietal lobes and visual fields. Visual fields can be tested in children less than a year of age by having one examiner attracting the attention of the child to a toy after which another examiner in back of the child brings another toy into the field of vision, with the location at which the child turns his or her head towards this second toy noted. The blink reflex, which is where an object is rapidly brought close to the child's eyes, appears at about 3 to 4 months. It is present in about 50% of babies at 5 months, and 100% of children at 12 months.

CN III, IV, and VI (oculomotor, trochlear, abducens) can be checked by extraocular movements and pupillary size and reaction to light. Pupils may be large and not responsive to light in babies earlier than 30 weeks gestation. A mnemonic to remember the cranial nerves which innervates the extraocular muscles is the formula (LR6 SO4). CN 6 innervates the lateral rectus, CN 4 innervates the superior oblique, and CN 3 innervates the other ocular muscles.

The Doll's eyes phenomenon can also be used to assess extraocular movements in a comatose patient with an intact brainstem. In these patients, horizontal eye movements can be elicited when the head is suddenly turned to one side resulting in the eyes moving to the opposite side in a symmetrical fashion. Also, vertical eye movements can be demonstrated by rapidly moving the head up and down, with the eyes moving in the opposite direction of the head, again in a symmetrical fashion. If a patient were brain dead with no brainstem function, then no Doll's eyes movement would be seen. In effect, the eyes would be stationary when the head is turned. In conscious patients, the cerebrum would interfere with the Doll's eyes phenomenon. Although the Doll's eyes phenomenon can determine whether the brainstem is still functional, a better test would be to do cold calorics. In order to do this test, 5 mL of ice water is squirted into the external ear canal in comatose patients or 0.5 mL in alert, awake patients, and the action of the eyes are noted. There are three possible responses to this test. In the comatose patient with an intact brainstem, the eyes move in the direction of the stimulus. In alert, awake patients, there is nystagmus with the quick component in the opposite direction of the stimulus. Lastly, in patients without a functioning brainstem, there is no movement of the eyes when cold calorics are performed. One needs to remember that cold calorics do not test for extraocular movements, but for vestibular function (CN VIII).

A special note about pupils is inserted here because of a common medical student error. PERRLA stands for pupils equal round and reactive to light and accommodation. Some individuals write PEARL which might stand for pupils equal and reactive to light. The latter is probably satisfactory although it might be better to write PERRL (leave out the A). The accommodation reflex is difficult to see on light eyed individuals, it is impossible to see on dark eyed individuals, and it is impossible to accomplish on non-cooperative subjects such as infants and toddlers. Thus, to write PERRLA on a 6 month old or a comatose patient is an obvious error. If you are in the habit of writing PERRLA, ask yourself this. Do you really check the accommodation reflex and did you really, truly see the proper reaction? What is the clinical utility of checking the accommodation reflex? It has almost no clinical utility other than to identify the Argyll Robertson pupil of neurosyphilis. In the medical malpractice literature, a chart entry such as "PERRLA" has been used to discredit the physician's credibility since a jury can be easily convinced that the accommodation reflex was not or could not be done. If you still believe that you must do the accommodation reflex, then you should write "PERRL + intact accommodation" and note the patient's eye color, to show that you really did it. A medical student once saw a patient for fever and in the PMH, he wrote that the patient has a glass eye because of a traumatic injury. The exam section of his note indicated: PERRLA. Be careful, the pupil of the glass eye does not react to light, nor accommodation.

CN V (trigeminal) is assessed by checking the sensation of the face. Noting the action of the temporalis and masseter muscles can test the motor roots of this cranial nerve. The corneal reflex also checks the ophthalmic branch of CN V. CN VII (facial nerve) dysfunction is seen with facial asymmetry. Taste in the anterior two-thirds of the tongue is innervated by the chorda tympani branch of VII, and can be checked by applying salt or sugar solutions by cotton-stick applicators. CN VIII (auditory) which conducts cochlear and vestibular function can be tested by the child's response to a bell or by recalling a whispered word or number. Noting the eye movements after turning the child several times in a clockwise and counterclockwise direction can check vestibular function. CN IX, X (glossopharyngeal, vagus) function is determined by the position of the uvula and palate. If there is a vagal nerve problem, the uvula will deviate toward the unaffected side, and the palate will move away from the affected side. The gag reflex actually tests parts of IX and X, since IX is the afferent sensory limb (sensory to the back of the pharynx) and X controls the muscles of the pharynx and elevation of the palate. CN XI (spinal accessory) is tested asking the patient to turn his/her head against resistance, which involves the sternocleidomastoid muscle. CN XII (hypoglossal) dysfunction is seen when the tongue deviates toward the affected side.

The above tests should be considered basic. Several cranial nerves cannot be tested fully since they have multiple functions. For example, the multiple functions of CN X (vagus) cannot be tested fully and we really don't check CN IX's sensory limb from the carotid sinus function. Thus it would be less than truthful, if one wrote down "cranial nerves intact", "CNs II-XII intact", or "cranial nerves grossly intact". These statements are actually assessments rather than descriptions of observations which is what the physical exam should state. Additionally, it would not be possible to honestly state that the cranial nerves are intact since several cranial nerve functions were not tested (because they cannot be easily done). For example, to assume that CN X is intact just because the patient gags is a bit of a stretch. The term "grossly intact" usually means that a cranial nerve exam was not done, but the patient's facial function is symmetric. Perhaps it would be more honest to state that the "the patient's facial function is symmetric". In the medical malpractice literature, statements such as "CNs II-XII intact" have been used to question the credibility of the physician's chart entries since a jury can be easily convinced that an exam to support such a statement is not easily done.

Motor System (2). Observing the child's posture and simple maneuvers such as retrieving a ball or running outside the examination room can check motor integrity. The following grading system can be used for assessing muscle strength:

0 - No muscle contraction
1 - Flicker or trace of contraction
2 - Active movement without gravity
3 - Active movement against gravity
4 - Active movement against gravity and resistance
5 - Normal strength

A sensitive test to assess the strength for the upper extremities is the pronator sign. Have the child raise his/her arms and note the position of the arms. Weakness of the arm is seen by hyperpronation and elbow flexion. Strength of the flexors of the knee can be tested by the Barré sign, which is performed by having the child keep both knees at right angles while lying prone.

Cerebellar function (2). Observing how a child reaches for and manipulates toys can check for coordination. Other tests include finger-to-nose and heel-to-shin. Rapid pronation and supination of the hands, or rapid tapping of the foot can assess for dysdiadochokinesia, or the impairment to perform rapidly alternating movements indicative of cerebellar dysfunction.

The Romberg test is often mistaken to be a test for cerebellar function, but it is actually a test of proprioception (dorsal columns). This test is done by asking the patient to stand with his arms outstretched forward. He must close his eyes and rely on proprioception to keep his body erect and balanced (without any visual information). He can be gently pushed to see if he can maintain balance.

Sensory. This can be assessed in an older child by pinprick, light touch, position, and vibration sense. Object discrimination, which tests for higher cortical functions, can be done using coins, paper clips, or rubber bands.

Reflexes. The segmental levels of major deep tendon reflexes are: Jaw jerk (CN V), biceps (C5-6), triceps (C6-8), brachioradialis (also known as the radial periosteal, C5-6), patellar (also know as quadriceps, L2-4), ankle (also known as Achilles, S1-2). The best known sign of pyramidal tract dysfunction is the Babinski's sign. This sign can be elicited when the plantar surface of the foot is stimulated with a stiff object (e.g., key) from the heel through the lateral aspect of the foot, crossing over the distal metatarsals, ending in the big toe. A positive Babinski's sign is seen when there is dorsiflexion (extension) of the great toe and fanning of the toes. This response can be normally seen in children up to 2 years of age or sometimes after a seizure. A positive Babinski's sign is also called an upgoing plantar reflex, as opposed to the normal downgoing plantar reflex which is called a negative Babinski's sign. Another sign is clonus that can be tested by maintaining dorsiflexion of the foot. Sustained clonus is abnormal at all ages and signifies a lesion in the pyramidal tract or the cortical origin of the pyramidal tract.

Neurological examination of the infant. The neurological examination of the infant can be organized in the following fashion: 1) Posture and muscle tone, 2) Primitive reflexes, 3) Age invariable items.

Posture and muscle tone. This can be divided in three ways: 1) resting posture, 2) passive tone, 3) active tone. Resting posture can be performed by observing the infant undressed. The infant should have flexion of the elbows, hips, and knees (varying with age). Hypertonia in the extremities decreases after 3 months of age, with the upper extremities then the lower extremities. At the same time, tone in the trunk and neck increases. Passive tone is done by determining resistance of passive movements of the joints while the infant is awake and not crying. One can do this by flapping the hands and feet, and by other maneuvers. The scarf sign is where the arm is pulled across the chest and if the elbow passes the midline, then hypotonia is present. Active tone can be assessed by the traction response up to 3 months of age. The infant's hands are held with the examiner's thumbs in the infant's palms, and the fingers around the wrists. The infant is slowly pulled to a sitting position. Normally the elbows flex and the neck raises the head. If hypotonia is present, then the head lags backward, then as the erect position is assumed, the head then drops forward. If hypertonia is present, the head is maintained backwards.

Primitive reflexes. Primitive reflexes are usually present from the time of birth and represents spinal reflexes until the infant becomes older and higher cortical functions suppress them. Although there are many types of reflexes, it would be a good idea to do some of them and not necessarily all since they would not give more information than what was already done.

Vertical suspension. The infant is suspended by holding the chest with both hands and lifting the patient in an upright position, with the legs dangling. If scissoring or hyperextension of the legs is seen, then spasticity is present. If there is scissoring of the legs, then spasticity may be present making it suspicious that cerebral palsy may be present.

Horizontal suspension (Landau reflex). To perform this reflex, the infant, while prone with the examiner's hand under the trunk, is gently lifted upwards. Normally, the spine extends a little so that the eyes are looking just below the horizontal. If the body collapses into an upside down "U" shape, then hypotonia is present.

Segmental medullary reflexes. An example is the sucking reflex that involves afferent fibers of CN V and IX, and efferent fibers of CN VII, IX, and XII.

Moro reflex. This is done by having the head hyperextended, falling back about 3 centimeters in relation to the trunk. A normal response is seen when the infant opens his hands, extends and abducts the arms, and then brings them together, followed by a cry. It is present in all newborns and disappears before the age of 6 months.

Tonic neck response. Also called the fencer's stance, this reflex can be elicited when the head is turned to the side while the rest of the body lies flat on the table. A normal response is extension of the arm and leg on the side that the head is turned, and flexion of the arm and leg on the opposite side (similar to a fencing stance). Abnormal responses occur when this response is sustained or if it occurs

differently when the head is turned to the right or left (i.e., the response is not the same when tested on both sides). It usually disappears about 6 to 7 months of age.

Palmar and plantar grasp reflexes. They are performed by applying gentle pressure to the palm or sole. An abnormal response occurs when this response is absent before 2 to 3 months of age, persistence after this time, or asymmetry.

Parachute response. The infant is suspended horizontally with the face down, and is brought quickly down toward the floor, making sure that the infant is firmly held. A normal response is seen when the arms are extended and the hands open.

Reflex placing and stepping responses. Reflex placing is seen when the dorsum of the foot is placed against the edge of the examination table. Reflex stepping is seen when the sole of the foot is placed on the table, and the infant appears to be walking. This reflex disappears at about 4 to 5 months of age.

Questions

1. Name the steps involved of the older child's neurological examination.
2. Name five primitive reflexes.
3. What extraocular muscles are innervated by abducens and trochlear nerves?
4. What does optokinetic nystagmus signify? When can it be performed in an infant?
5. What is the pronator sign? What does it test for?
6. In what two instances can a positive Babinski's sign be seen in normal patients?

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4. Tottori M. Personal communication, 2001. A black sheet paper is used and multiple strips of white tape (about 2 cm wide) are attached so that there are alternating strips of black and white. A photocopy of this is made and is then wrapped around an empty soda can. A straight piece of metal, such as from a dressing hanger, is used to pierce the top and bottom parts of the can and is thus the handle to rotate the drum.

I would like to thank Dr. Yoshio Futatsugi for his review of this chapter. His assistance is greatly appreciated.

Answers to questions

1. Examination of the skull, cranial nerves, strength, cerebellar function, sensory, and reflexes.
2. Ventral suspension, horizontal suspension (Landau reflex), Moro reflex, tonic neck response (fencer's stance), palmar and plantar grasp reflexes, parachute response, reflex placing and stepping responses.
3. Lateral rectus and superior oblique muscles, respectively.
4. Signifies that cortical vision is intact, in addition to showing the integrity of the frontal and parietal lobes, and visual fields. It can be performed at about 4 to 6 months of age.
5. When the arms are lifted, a positive sign is when an arm is hyperpronated with the elbow flexed. It tests for strength of the upper extremities, and a positive sign signifies weakness.
6. In what two instances can a positive Babinski's sign be seen in normal patients? In newborns up to 2-1/2 years of age and sometimes in patients just after a febrile seizure.

Chapter XVIII.2. Cerebral Palsy
Mari Uehara, MD

Roy is a 13 month old male who has been followed in the Pediatric outpatient clinic. He was born at term by normal vaginal delivery without complications and his birth weight was 3300g. His mother did not have any problems during the pregnancy. At 6 months of age, you noticed his head control was poor. Currently, he calls everyone "mama" and follows one-step commands. He is able to drink from a cup. He is able to roll over from his stomach to his back but he is not able to sit or stand. His height and weight are both between the 25-50th percentiles and his head circumference is within 2 standard deviations of the mean. Some primitive reflexes such as the Asymmetric Tonic Neck Reflex (ATNR) persist and he has increased muscle tone, especially in his legs. His deep tendon reflexes are exaggerated.

Cerebral palsy (CP) is defined as a non-progressive, but often clinically changing motor impairment due to an abnormality of the developing brain. It is a symptom complex or a descriptive term rather than a specific disease. Intellectual, sensory, and/or behavioral problems may also exist although the primary abnormality must be a motor deficit. The prevalence is estimated at about 2 per 1000 early school aged children (1).

In more than 50% of the children who have CP, an etiology may not be evident (1). The insult to the brain may occur prenatally (e.g., congenital malformation, intrauterine infections, teratogens), perinatally (e.g., birth trauma, anoxia), or postnatally (e.g., infections, accidental or non-accidental trauma, intracranial hemorrhage). The majority of the cases are not caused by hypoxic ischemic incidents occurring perinatally as it was believed until recently. 70-80% cases are prenatal in origin (3). Infants who weigh less than 1500g at birth have a 10% to 20% risk of developing CP (2). Although prematurity is the most common known antecedent of CP, the majority of children who develop CP are born at term.

CP is often classified according to the predominant type of motor impairment: spastic, dyskinetic, ataxic, or mixed. Spastic CP is the most common type and affects 70-80% of individuals with CP. It is characterized by a generalized increase in muscle tone. CP can be further classified based on which limbs are involved, the suspected etiology or functional capacities. For example, in spastic diplegia, the lower extremities are more involved than the upper extremities. In hemiplegia, one side of the body is more involved. All the extremities and often trunk and oral motor function are also affected in spastic quadriplegia.

Choreoathetoid CP is a subtype of dyskinetic CP. Athetosis are slow writhing involuntary movements and involves distal limbs. Choreiform movements are asymmetric, uncoordinated, involuntary muscle contractions. These movements are more prominent under stress and their intensity may change. It may not be apparent until about 12 to 18 months of age when a toddler starts to show athetoid or dystonic posturing on voluntary movements. One known cause of this form of CP is encephalopathy associated with very high bilirubin levels during the neonatal period.

Ataxic CP is characterized by cerebellar dysfunction. This is the least common type with a frequency of 1% among individuals with CP. Mixed CP involves both symptoms of upper motor neuron and extrapyramidal symptoms. For example, a child who has spastic quadriplegia may also have choreoathetoid movements.

The diagnosis of CP is essentially clinical and depends on knowledge of normal development and its variation. While no factors or combination of factors is an absolute predictor of CP, certain situations warrant closer monitoring. It is also important to remember that the neurological picture may change as the child grows older and the CNS matures. It is often difficult to diagnose children with CP before 6 months of age.

During infancy, feeding difficulty is an important sign. A child may continue to need gavage (tube) feedings. He or she may be difficult to feed, or require an excessive amount of time for feeding. A child may have failure to thrive or a poor rate of head growth due to a serious insult to the brain. Constipation is another symptom among infants with CP. He/she may be quiet and very easy, or irritable during infancy. The child may show a premature handedness preference during the first 18 months of life. This can be an early sign of hemiplegia.

There are several useful parameters for the assessment of neuromotor function.

A) Muscle function: Muscle tone and strength should be examined. By simple observation, you may be able to see poor head control, scissoring of the lower extremities, or flexor posturing of upper extremities.

B) Patterns of movement should be assessed. There are three patterns of movements: 1) Normal movements, 2) Abnormal movements which are never seen in normally developing children (e.g., restricted movements in children with spastic diplegia or hemiplegia, or involuntary movements seen in children with athetoid CP), 3) Atypical movements which may be seen in normally developing children (e.g., bouncing along the floor while supine, or log-rolling as methods of mobility).

C) Structure or alignment of the body. A child with spastic CP may have dislocation of the hip due to adductor and abductor muscle tone imbalance and resultant poor joint development. Children with spastic CP also have the tendency for plantar flexion of the feet. Scoliosis can be a problem for all children with CP.

D) Reflexes should be assessed. Physicians are generally very familiar with the deep tendon reflexes. Of equal significance are so-called developmental reflexes. Children with CP may have persistent primitive reflexes such as the Moro reflex and the asymmetric tonic neck reflex (ATNR). Also, children with CP may present with delayed emergence of righting reactions (natural tendency to position the body/head upright) and protective/equilibrium responses (e.g., parachute reflex) as signs of delayed maturation or CNS injury.

E) Gross motor skills are usually affected but other developmental milestones should be also assessed to determine if delays are more global.

Many co-existing conditions are frequently seen in children with CP. These may include sensory impairments, seizures, cognitive impairment, orthopedic problems, impaired speech and language, feeding issues, dental problems, skin breakdown and respiratory infections. Because CP is the result of an insult to the developing brain, some of these problems may not be treatable or they may only partially respond to medical/surgical treatment. The treatment plans and programs must be individualized and modified over time as the child grows.

Children with CP have a high incidence of visual impairments (4,5). They may have refractive errors, visual fields defects, or cortical blindness. Strabismus is very common and may lead to the development of amblyopia. There is also an increased incidence of sensorineural and conductive type hearing impairment. Hearing impairments can further delay speech and language development of children with CP.

25-50% of children with CP may also experience seizures (4,5). Seizures are most commonly seen among the children with spastic quadriplegia and hemiplegia. Generalized tonic-clonic and partial seizures are the common types. Approximately half of the children with CP have mental retardation. Although children with more severe motor involvement tend to have mental retardation more frequently, this is not always the case. Among children with normal intelligence, there is a higher incidence of learning disabilities. Feeding difficulties (e.g., with sucking, chewing, and/or swallowing) are common among children with CP as a result of impairment of oral motor muscle function. This may also cause problems with speech articulation. Drooling and gastroesophageal reflux may also occur. Aspiration can cause pneumonia which is the leading cause of death in children with CP.

Because of the difficulties in motor control, assistance is needed to maintain good posture and alignment and good range of motion of the joints. Subluxation or dislocation of the hip are common in children with CP. The incidence is higher among children with spastic quadriplegia. Dislocated hips can develop arthritis and severe pain. Poor posture or positioning can result in scoliosis due to the unequal muscle tension. Spasticity and limited muscle use may lead to contractures. The interventions used to treat these conditions include physical therapy, orthopedic surgery, muscle tone management (e.g., intrathecal Baclofen infusion), and orthoses (e.g., ankle-foot orthosis, body shell).

The life expectancy of children with CP depends on the type and the severity of the condition. Although the projected life span of children with CP is less than that of the general population due to complications of motor dysfunction, the majority of affected children will survive well into adulthood if given appropriate medical attention.

The prognosis regarding ambulation is also dependent on the type and the severity of the motor dysfunction. Overall, children with hemiparesis will walk by 18 months to 36 months. With or without assistive devices, 80-90% of children with diplegia, 70% of children with dyskinesia and 50% of children with quadriplegia may achieve some degree of ambulation (1). Ambulation may be predicted based on the achievement of motor milestones. For example, there is a good prognosis for attaining some ambulation if a child is able to sit independently by 24 months.

Because of multisystem involvement and various psychosocial and medical needs, no one discipline can assess and manage all aspects of the child with CP alone. It is important to be interdisciplinary to have a successful management program. The child's physician has to be familiar with community resources such as early intervention programs and support groups. It is important for the primary care physician to communicate with the therapists, specialists, and school personnel. The physician needs to advocate for the necessary services for the child and his/her family. Primary care physicians should be aware of the different problems and needs that the children experience as they get older and help them transition from the toddler to school age to adulthood as smoothly as possible. The goal for the treatment program is to maximize function and optimize development to help them participate in as many activities as possible in multiple social settings.

Questions

1. Cerebral Palsy may have changing clinical features in: (select one)
    a. The brain abnormality.
    b. Effects on the motor system.
    c. That seizures are usually not treatable after a few years.
    d. Subtypes - first a person has the choreoathetoid type, then the spastic type, and then becomes quadriplegic.
    e. Decrease in IQ over time.

2. Currently, most cases of cerebral palsy with a known etiology are thought to be
    a. Prenatal in origin.
    b. Perinatal in origin.
    c. Postnatal in origin.

3. What is the most common type of cerebral palsy?
    a. Spastic
    b. Choreoathetoid
    c. Ataxic
    d. Mixed
    e. All are equally common

4. Which of the following is NOT a worrisome sign that may indicate cerebral palsy?
    a. Poor rate of head growth
    b. Hand preference at 6 months of age
    c. Scissoring of the legs
    d. Obesity
    e. High muscle tone

5. True/False: Because of the neuromotor dysfunction and associated conditions, children with cerebral palsy rarely live into adulthood.

6. True/False: Children with hemiplegia have a higher rate of ambulation than diplegia and quadriplegia

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Answers to the questions
1.b, 2.a, 3.a, 4.d, 5.false, 6.true

Chapter XVIII.3. Febrile Seizures
Vince K. Yamashiroya, MD

An ambulance brings a 15 month old boy to the emergency department with a seizure associated with fever. He has been in good health except for a high fever that developed today to about 103-104 degrees. His mother gave him a small dose of acetaminophen. About 20 minutes ago when the mother was checking up on her child, she noticed shaking of the arms and legs and his eyes had a blank stare. This went on for what seemed like 5 minutes. She called 911 and an ambulance was dispatched. He has been ill with a high fever today and a slight cough and mild nasal congestion. Just prior to the seizure, he was playing with some toys. There is no vomiting, diarrhea, rash, or fussiness.

Past medical history is unremarkable.

Family history is significant for an uncle who has epilepsy.

Exam: VS T 39.8 degrees C (103.6 degrees F), P 165, RR 30, BP 90/60, O2 sat 100% on RA. He is clingy, alert to his surroundings, and otherwise is in no distress. His mother appears anxious and there appears to be good bonding between her and her child. Skin is without bruising or neurocutaneous stigmata. Anterior fontanelle is closed. Pupils are equal and reactive. EOMs are conjugate. The red reflex is present bilaterally. There is no sunsetting of the eyes. TMs are normal. His mouth exam shows moist mucosa without erythema. The Brudzinski and Kernig signs are difficult to assess. Respirations are regular. Neurologically, he moves both arms and legs equally. His tone appears normal. The rest of the examination is normal.

Febrile seizures are broadly defined as seizures occurring in the presence of fever, but in the absence of central nervous system (CNS) infection, in children ages 6 months to 5 years of age. It is the most common reason for convulsions in children less than 5 years of age, and they occur in 2 to 5% of all children, although it has been reported to be more frequent in Asian countries. In Japan, the rate has been reported to be 7% and in the Mariana Islands 14%. It is thought that the rates in these areas are higher because some of the common infections of childhood may occur earlier in life when children are most susceptible to febrile seizures. Also, since more families sleep in the same room, this may make recognition better than in Western countries (1). The age at which febrile seizures most frequently occur is in the second year of life, and they occur slightly more commonly in boys than in girls. Febrile seizures can be divided into two types: simple and complex. Simple febrile seizures are characterized by the following: duration less than 15 minutes, and generalized. Complex febrile seizures have the following features: duration greater than 15 minutes, multiple within 24 hours, and/or focal (2).

The risk of recurrence after the first febrile seizure is about 33%, and about 9% will have three or more recurrences. The risks for recurrence are: occurrence of the first febrile seizure at a young age; family history of febrile seizures; short duration of fever before the seizure; relatively low fever at the time of the initial seizure; and possibly a family history of an afebrile seizure. It has been observed that the time of recurrence is usually within the first year of onset. Although complex febrile seizures are not usually associated with recurrent febrile seizures, they may be a risk factor for epilepsy later in life. Febrile seizures seem to run in families, but their mode of inheritance is unknown. The risk for other siblings developing febrile seizures is about 10-20%, but may be higher if the parents also have a history of febrile seizures themselves (2).

Febrile seizures usually occur in the first 24 hours of the onset of fever. It has been suggested that it is the rapid rise in the child's temperature, which causes a febrile seizure rather than the actual height of the fever itself; however, there is no substantial proof to support this suggestion. The seizures are usually generalized and tonic-clonic, but other types may be present as well. Parents may describe stiffening, jerking, apnea, cyanosis and incontinence, usually followed by drowsiness (commonly called post-ictal for short). There may be variations to this such as staring without stiffness, jerking movements without prior stiffening, and localized stiffness or jerking. Simple, benign febrile seizures should be short, usually 1 to 2 minutes, but some may be longer (up to 15 minutes). Because of the short duration, medical attention usually occurs after the seizure has ended (2).

Although the diagnosis of febrile seizure is likely in a 6 month to 5 year old with fever and a convulsion, one should consider other causes such as meningitis, encephalitis, Shigella gastroenteritis, medications/toxins (such as diphenhydramine, tricyclic antidepressants, amphetamines, and cocaine), hypoglycemia, electrolyte abnormalities (that could be due to dehydration), shaken baby syndrome, accidental head trauma, and epilepsy (2). Many of these other diseases can be ruled out by a good history, physical examination, and clinical appearance after the seizure has ended.

How should these patients be managed in terms of diagnostic work-up and treatment? Given that febrile seizures are a relatively common phenomenon, should every child with fever and seizures have a lumbar puncture done to rule out meningitis, or CT scan and EEG to look for CNS abnormalities? The American Academy of Pediatrics attempted to answer this in two practice parameters on the evaluation and treatment of children with febrile seizures that were published in 1996 and 1999 (3,4). The recommendations of these two practice parameters are listed below. It should be kept in mind that these are guidelines only and that each case should be individualized according to the particular child, and the situation. One should remember that these guidelines are written for practitioners with a wide range of experience and training; therefore, the points mentioned here are meant to be conservative. Also these guidelines are written for children from 6 months to 5 years of age who had a simple febrile seizure and are neurologically normal. The guidelines do not include children with complex febrile seizures.

1. Lumbar puncture. An LP should be strongly considered in all infants less than 12 months of age because signs and symptoms of meningitis may be minimal or absent in this age group. An LP should be considered in children between 12 months to 18 months of age, since signs of meningitis might be subtle. An LP does not need to be done in children older than 18 months unless they show signs of meningitis (neck stiffness, Brudzinski and Kernig signs) or have symptoms of a CNS infection. Infants and children who were treated with

antibiotics prior to the seizure should be strongly considered to have an LP done. This is because antibiotics can mask the signs and symptoms of meningitis (partially treated meningitis). Even if an LP is performed and the results are negative, it is still prudent to be cautious and vigilant since spinal fluid may be normal in the early stages of meningitis (3). The clinical appearance of the child after the seizure has ended plays a very significant role, in that the playful, active child who appears normal, probably does not have meningitis.

2. EEG. An EEG does not need to be performed as part of the work-up for a first time simple febrile seizure. Although the EEG may be abnormal (occipital slowing) in the first month after the seizure, there has been no correlation of this to recurrence risk or the risk for developing epilepsy in the future (3,5). An EEG done 4 to 6 weeks following the seizure should be normal. If it is not, then epilepsy is more likely. In clinical practice this is not usually done after a single simple febrile seizure since an EEG is difficult to do in young children and 4 to 6 weeks have passed, presumably without any more seizures.

3. Laboratory studies. Laboratory tests, such as a CBC, serum electrolytes, calcium, magnesium, phosphorus, and glucose, need not be done routinely. It should instead be tailored to the presenting symptoms. For example, electrolytes and glucose can be checked in a patient who is vomiting.

4. Neuroimaging. CT scan of the head does not need to be done routinely. There is no data available showing that children with febrile seizures have an increased incidence of CNS abnormalities, nor any evidence that febrile seizures lead to structural brain damage.

Recommendations are not as clear-cut for children who develop complex febrile seizures; however, the threshold for performing blood tests, neuroimaging, and EEG is lower. A lumbar puncture should be strongly considered if the patient is young, if there are signs and symptoms of meningitis, if the patient is already on antibiotics, if there is no rapid improvement, or if the patient does not regain full consciousness (5).

If the child develops another seizure, then supportive measures are recommended. During the time the seizure is occurring, the patient should be placed on his/her side to prevent aspiration, and the airway should be maintained. Also nothing should be placed in their mouths. If it is prolonged, then diazepam (Valium) should be given either intravenously or rectally. If the patient has a fever, avoiding overheating by removing blankets and heavy clothes can prevent febrile seizures, in addition to administering antipyretics such as acetaminophen and giving cool baths. Diazepam can also be used to prevent future recurrences of febrile seizures for the next several hours, although its administration as a preventive measure is controversial (5).

Should a patient be hospitalized? Probably not, although it depends what the circumstances are. It is recommended that patients who had a febrile seizure be observed in the emergency department for several hours and reevaluated. After this time, most children would have improved, and if the cause of the fever is known and treated, they can then be sent home. Similarly, in a doctor's office, they can be observed if they are rapidly improving. If they are not improving, then the diagnostic studies mentioned previously should be considered. Circumstances when they should be hospitalized for overnight observation are: the clinical situation is still unstable, there is a possibility of meningitis, and/or the parents are unreliable or unable to cope with the child developing another seizure (1).

An essential component of management is parental counseling. Reassurance should consist of three components. First, parents should be reassured by informing them that although the febrile seizure is frightening, it will not cause brain damage, and the possibility of their child developing epilepsy is small. Secondly, they should also be told that there is a possibility that it could happen again, especially in the first 24 hours. Also one third of children will have at least another febrile seizure later, with most occurring within one year of the episode. Thirdly, if a seizure occurs, the child should be kept on his/her side, and they should observe their child. If the seizure does not stop in 3 minutes, then emergency medical services should be contacted (1).

Long-term pharmacotherapy is probably unnecessary, especially for simple febrile seizures. Although the AAP Practice Parameters discourage use of anticonvulsants in simple febrile seizures, it does mention that giving diazepam during the start of fever in patients with parents having high anxiety is an option. Diazepam is given orally using a dose of 1 mg/kg/day in three divided doses when the child is febrile. Disadvantages of using diazepam are lethargy, drowsiness, ataxia, and masking of a CNS infection. Other medications that have been used to prevent recurrences are phenobarbital and valproic acid. A dose of 5 mg/kg/day of phenobarbital is given once to twice a day. Although they can prevent 90% of recurrences of febrile seizures, they are not without significant side effects. Phenobarbital has been associated with behavioral problems (hyperactivity) and hypersensitivity reactions. Valproic acid has a risk of developing fatal hepatotoxicity, thrombocytopenia, weight changes, gastrointestinal problems, and pancreatitis. These medications have been considered in those patients who have focal paralysis after a seizure, multiple seizures in a young child, and high parental anxiety despite reassurance (1,4). Phenytoin and carbamazepine have no demonstrated efficacy in preventing febrile seizures.

Despite the frightening appearance of the episode, and the parental belief that their child is going to die, simple febrile seizures remain a benign condition with the majority of children having no neurological sequelae. In other words, it does not lead to brain damage or cognitive abnormalities. Although the risk of developing another febrile seizure is moderate, the possibility of epilepsy is very small. For this reason, long-term therapy anticonvulsant therapy is not usually recommended, but practitioners should provide reassurance, education of what to do when their child has another febrile seizure, and antipyretic therapy when a fever is present.

I would like to thank Dr. Yoshio Futatsugi for reviewing this chapter and Dr. Robert Bart for his helpful suggestions and input.

Questions

1. At what ages do febrile seizures occur? How common is this problem?
2. In what percentage of patients will febrile seizures occur a second time?
3. What are the differences between simple and complex febrile seizures? Why is it important to know this distinction (think of recurrence risk of febrile seizures, development of epilepsy, and work-up)?
4. A febrile seizure is a diagnosis of exclusion. What other diagnoses should be considered in a child with fever and seizures?
5. According to the guidelines put forth by the American Academy of Pediatrics' Practice Parameter, who should be strongly considered to receive a lumbar puncture?
6. Most patients with febrile seizures can be discharged home. What are three indications for a child who should be hospitalized for overnight observation?
7. Although diazepam (Valium) can be used to prevent recurrences when given at the start of a febrile illness, what are its disadvantages?
8. A key part to management is reassurance. What are three ways parents should be reassured and educated?

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Answers to questions

1. 6 months to 5 years. It occurs in 2-5% of all children and is the most common reason for convulsions in children less than 5 years of age.
2. 33%.
3. Simple seizures are characterized by being less than 15 minutes duration and generalized. Complex febrile seizures are greater than 15 minutes duration, multiple within 24 hours, and focal. Simple febrile seizures have a higher risk for febrile seizures. Complex febrile seizures have a higher risk for epilepsy. One should have a lower threshold for performing tests and hospitalization in cases of complex febrile seizures.
4. Meningitis, encephalitis, Shigella gastroenteritis, medications and toxins, hypoglycemia, electrolyte abnormalities, shaken baby syndrome, accidental head trauma, and epilepsy.
5. Infants less than 12 months of age.
6. Unstable clinical situation, possibility for meningitis, and parents unreliable or unable to cope with the child developing another seizure.
7. Disadvantages include lethargy, drowsiness, ataxia, and masking of a CNS infection.
8. 1) Seizure will not cause brain damage and the risk of a child developing epilepsy is small. 2) Possibility that it can happen again, especially in the first 24 hours. One third of children will have at least another febrile seizure with most occurring within one year of the episode. 3) If seizure occurs again, child should be kept on his or her side. If seizure does not stop within 3 minutes, then emergency medical services should be contacted.

Chapter XVIII.4. Epilepsy

Keith K. Abe, MD, MS

A previously healthy 9 year old boy is brought to the emergency department because of the sudden onset of left-sided paralysis. His parents were aroused at night by a thrashing noise from his bedroom. They rushed to his room and found his bedsheets awry. He was lying in bed, breathing deeply, difficult to arouse, and could not stand or move his left arm or leg. There was no prior history of trauma, but he was noted to have a small tongue laceration. There is no history of toxic ingestions, fever, emesis or incontinence. EMS was called and he became more arousable during transport.

PMH is negative for any seizures or other serious medical conditions. His development has been normal. Family history is negative for seizures, strokes or brain tumors. His social history is negative for any problems at home. He is doing well in school.

Exam: Vital signs are normal. He is now alert, oriented, lying supine and not moving his left extremities. He appears non-dysmorphic and non-toxic. His head appears normal and without trauma other than the tongue laceration. Neck is supple with full range of active motion. No Brudzinski or Kernig signs. Pupils are equally round and reactive to light. Extraocular movements are intact. No facial asymmetry. His heart is regular without murmurs. Lungs are clear. Abdominal exam is unremarkable. Skin is without neurocutaneous stigmata or signs of trauma. Neurologic evaluation reveals decreased strength (grade 2 out of 5) on the left. No sensory loss. Deep tendon reflexes are more brisk on the left and a Babinski sign is present on the left as well. Coordination is intact on the right. Coordination on the left and gait are not tested.

Labs: CBC and electrolytes are normal. Glucose is slightly elevated. CT scan of his head is normal.

He is hospitalized for observation. The next day, his left-sided weakness and neurologic abnormalities on exam have resolved. An EEG reveals centrotemporal spikes. After a discussion with his parents, it is decided to discharge him on no anticonvulsant medications. It is concluded that his lethargic episode was due to an unwitnessed seizure with subsequent post-ictal drowsiness.

A second nocturnal seizure occurs a year later, and he is started on carbamazepine. Over the next two years, he experiences no further seizures. He is treated until age 12 when his medication is weaned off and he does well thereafter.

A seizure is a sudden, involuntary, stereotypical, repetitive alteration in behavior, including a change in motor activity, in autonomic function, in consciousness, and/or in sensation, which is caused by hypersynchronous discharges from a group of cerebral neurons (1,2). Epilepsy is a condition in which an individual is predisposed to recurrent seizures because of a central nervous system disorder (although about two-thirds have no identifiable cause). Recurrent seizures are the symptomatic expression of underlying brain pathology, not a disease in the usual sense (3).

While all people with epilepsy have seizures by definition, not everyone who has a seizure has epilepsy. Four to six percent of all children will have at least one seizure in the first 16 years of life; however, most of these are benign febrile seizures, and the cumulative risk of epilepsy during this time is only about 1-2% (4,5). In other words, less than one third of children who experience a seizure ever develop epilepsy. Over one half of first-time seizures are simple febrile seizures (see the chapter on febrile seizures) and another third are single isolated seizure events or seizures associated with a non-epileptic medical illness. Overall, about half of the lifetime risk of

developing epilepsy is realized during the pediatric period, and it is the most common chronic neurologic disorder seen in children. Rates are highest during the first year of life.

As described, seizures are the clinical manifestations of epilepsy. Although other clinical manifestations may also be relevant, such as the neurologic exam, development, etc., this chapter will focus on general classifications and characteristics of epileptic seizures as proposed by the International League Against Epilepsy. Patients with epilepsy usually have a characteristic seizure type although some may have combinations of the following seizure types. The simplest classification is partial versus generalized. Partial seizures can be simple or complex. Generalized seizures can be absence or tonic-clonic. More classifications exist, but this chapter will focus on these four basic categories.

Partial or focal seizures are often caused by identifiable focal brain lesions which are related to the seizure activity expressed. They may be associated with an aura which is an altered sensation heralding or characterizing partial seizure activity. Any partial seizure can secondarily generalize into a tonic-clonic seizure which is discussed further below.

A simple partial seizure does not have an associated alteration of consciousness. Seizure manifestations may include tonic and/or clonic motor activity (e.g., originating from a contralateral motor cortex lesion), somatosensory phenomena (e.g., feeling a breeze, seeing light flashes, hearing buzzing, smelling odors, sensation of vertigo), and/or autonomic symptoms (e.g., gastric sensations, sweating, flushing). Of these, partial tonic-clonic seizures are the easiest to recognize. The others may be attributable to some other process and thus, are frequently not diagnosed as seizures.

Complex partial seizures also have focal origins but include an impairment of consciousness which implies alteration of functioning in the mesial temporal lobes, orbito frontal lobes, or in more widespread areas of the brain. The impaired consciousness is usually associated with a lack of understanding and memory of the brief event. They may involve more complicated behaviors such as frantic running, uncontrollable laughing, partial undressing, or facial automatisms. Partial complex seizures used to be called temporal lobe seizures because they often originate in the temporal lobes. Partial complex seizures also used to be called psychomotor seizures because they frequently include behavioral symptoms (e.g., auras, fear, déjà vu, facial grimacing).

Generalized seizures typically involve a loss of consciousness and/or a stereotypic motor activity. Absence seizures involve a few seconds of impairment of consciousness with eye blinking or staring which may occur as clustered events. Myoclonic seizures are usually seen in specific epilepsy syndromes and involve quick muscle jerks usually without associated impairment of consciousness. Tonic, clonic, or tonic-clonic seizures involve the abrupt onset of the described muscle activity for several minutes, often followed by post-ictal confusion and fatigue. Atonic seizures involve a sudden loss of postural tone, usually resulting in an abrupt collapse, which may not have any loss of consciousness. Generalized absence seizures are still sometimes called by their old name, petit mal seizures. These occur most commonly in the elementary school age group. Generalized tonic clonic seizures are still sometimes called by their old name, grand mal seizures.

Epileptic Seizure Classifications (1,5)

I. Partial
   A. Partial simple: Previous names include partial elementary seizures, focal motor seizures. Typical onset at any age.
   B. Partial complex: Previous names include temporal lobe seizures, psychomotor epilepsy. Typical onset at any age.
   C. Partial with secondary generalization: Previous names include Jacksonian march. Typical onset at any age.

II. Generalized
   A. Generalized tonic clonic: Previous names include grand mal seizures. Typical onset at any age.
   B. Generalized absence: Previous names include petit mal seizures. Typical onset at elementary school age.
   C. Other types including: myoclonic, tonic, clonic, atonic (akinetic, drop attacks).

III. Epilepsy syndromes: Seizure syndromes including: infantile spasms (also known loosely as West's syndrome, Salaam attacks, hypsarrhythmia on EEG), benign epilepsy of childhood (Rolandic), Lennox-Gastaut, and juvenile myoclonic epilepsy.

The differential diagnosis of seizures requires consideration on several levels. The first question needing to be answered is whether a seizure truly occurred. The history of the event may classically characterize seizure activity, or a patient may present in status epilepticus (see chapter on status epilepticus), in which case the answer to this question is clear. However, often times with non-medical personnel observing what seems to be seizure activity and the emotional anxiety that accompanies it, whether a seizure truly occurred may be unclear. Phenomena which may seem to be partial seizure-like activity include: tics, paroxysmal REM sleep behavior, benign sleep myoclonus (jerks as one falls asleep), night terrors, migraine, and benign paroxysmal vertigo. Phenomena which may seem to be generalized seizure-like activity include: syncope, breath-holding spells, panic attacks, psychogenic seizures/pseudoseizures/conversion reaction, gastroesophageal reflux, staring spells, and startle reflexes (infants).

Syncope is a common presentation which may be mistaken for a seizure. In general, syncope tends to be more gradual in onset, may be posturally related, and is without post-event focal neurologic findings or confusion. Seizures, however, are usually associated more with an abrupt onset, secondary injury, and may have post-ictal confusion, headache, incontinence or focal neurologic signs (e.g., Todd paralysis) as well as an abnormal EEG. Syncope may have some brief clonic or myoclonic extremity movements associated with it which can add to the confusion between the two types of events. In general, most true seizure motor activity does not have a reproducible trigger (e.g., a slamming door) and if the seizing body part is restrained, the seizure activity will persist.

If a seizure did occur, an important second question to be determined in evaluating a seizure is whether there were acute and reversible provocative causes such as: excessive stimulant medication or stimulant drug abuse, withdrawal from sedative drugs or alcohol, high fever (see chapter on febrile seizures), hypoglycemia, electrolyte imbalance (e.g., sodium, calcium, magnesium), hypoxia, or hypertensive encephalopathy. Answers to this question will play a pivotal role in selecting immediate therapy and determining future prognosis. Although a patient may have more than a single seizure attributed to these problems, these types of seizures would not typically be classified as epileptic.

A third question to be answered in the evaluation of what is determined to be a first-time, not acutely reversible seizure, is whether further seizures are expected to occur. This includes an evaluation to determine if the seizure is symptomatic of other pathology and could result in recurrent seizures (i.e., symptomatic epilepsy). These include the following:

Vascular etiologies:
- Arteriovenous malformation
- Aneurysm, subarachnoid hemorrhage
- Stroke
- Venous thrombosis
- Blood dyscrasias (eg sickle cell anemia)
- Vasculitides (e.g., SLE)

Infectious etiologies:
- Abscess
- Encephalitis, meningitis
- Rasmussen's syndrome (presumed viral)

Tumors and Congential etiologies:
- Heterotopias (refer to the chapter on developmental brain anomalies)
- Cortical dysplasias
- Neurocutaneous syndromes (e.g., Sturge-Weber, Neurofibromatosis, Tuberous Sclerosis, Ataxia-Telangiectasia, von Hippel-Lindau)
- Other intracranial neoplasms

Traumatic etiologies:
- Prenatal and perinatal (refer to the chapter on neonatal seizures)
- Child abuse
- Other head injuries

Less than 50% of patients with epilepsy have an identifiable cause. Those without a known underlying pathology are described as "cryptogenic" (likely an undetectable pathologic explanation) or "idiopathic" (presumed genetic) (1,4). Further consideration is also required to determine whether the seizure may be part of an epileptic syndrome which, by definition, would imply expected recurrent seizure activity without treatment. Epileptic syndromes in pediatrics are defined by known ages of onset, seizure patterns, EEG findings, and/or prognosis. These include: benign neonatal familial convulsions, infantile spasms (West's syndrome), benign childhood epilepsy with centrotemporal spikes, childhood epilepsy with occipital spikes, childhood absence, juvenile myoclonic epilepsy, and the Lennox-Gastaut syndrome. With all that has been mentioned, there are still numerous other epilepsy syndromes as well as combinations of seizures and EEG patterns which may not fit into the categories noted above.

All seizures involve abnormal paroxysmal hypersynchronous neuronal excitation. Cerebral manifestations include increased blood flow, increased oxygen and glucose consumption, and increased carbon dioxide and lactic acid production. If a patient can maintain appropriate oxygenation and ventilation, the increase in cerebral blood flow is usually sufficient to meet the initial increased metabolic requirements of the brain; however, prolonged seizures may result in permanent neuronal injury (2).

Systemic manifestations of massive sympathetic discharge may occur with seizures and include: pulse increase, BP increase, pupil dilatation, and increased blood glucose. Salivation may increase secondary to parotid stimulation with masseter muscle contraction. Respirations may cease or be irregular and the patient may have facial cyanosis due to a tonic increase in intrathoracic pressure and impeded venous return associated with maximal muscle group contractions. Failure of adequate ventilation can lead to hypoxia, hypercarbia, and respiratory acidosis. Prolonged skeletal muscle activity can lead to lactic acidosis, rhabdomyolysis, hyperkalemia, and hyperthermia.

Postictally (after the seizure event), effects of the massive neuronal depolarization and metabolic activity may include confusion, lethargy or a comatose state. Vomiting may occur, and patients with impaired consciousness may be unable to protect their airway and are at risk for aspiration. Impaired consciousness may also be associated with airway obstruction from the tongue or respiratory secretions. Head trauma may have precipitated a seizure event, but traumatic falls may also occur interictally and contribute to postictal altered mental status and other injuries.

Transient postictal focal deficits, e.g., Todd paralysis (transient paralysis which occurs after a seizure), may occur, but typically do not last beyond 24 hours. The mechanism is not well understood, but it may be attributed to neuronal dysfunction or neurotransmitter exhaustion. The duration and severity of the seizure do not correlate with the degree of postictal paralysis, and the paralysis is usually, but not always, noted in the area of the focal seizure activity (6).

Systemically in the postictal state, deep respirations may be present to compensate for respiratory and metabolic acidosis, and blood pressure and temperature quickly return to normal. Due to the catecholamine surge noted above, patients are usually mildly hyperglycemic. Headache and muscle soreness may also occur in association with muscle fatigue and acidosis.

The diagnosis of epileptic seizures involves determining: 1) if seizures occurred, 2) the type of seizures, 3) the cause of the seizures, and 4) if they are characteristic of an epileptic syndrome. Furthermore, any life-threatening causes of seizures (e.g., intracranial hemorrhage, meningitis/encephalitis, toxic ingestions), should be ruled-out or addressed in a timely fashion.

The history is the most important part of the diagnostic evaluation of a patient's seizure disorder. This may include:

Source: Reliable witnesses?

HPI: Seizure or not seizure? If a seizure, what type? Any complications?

Etiology: Provoked (trauma, drugs, fever)/unprovoked? Underlying seizure disorder, history of previous seizures or other neurologic disorder? If on an anticonvulsant drug (anti-epileptic drug or AED), has there been a change in dosing/compliance? Other signs of systemic illness or reasons for provocative causes: headache, vomiting, diarrhea, ataxia, altered mental status.

Onset: Prodromal symptoms (aura)? Rapid/gradual?

Characteristics: Partial/generalized? Duration (see chapter on status epilepticus if prolonged)? Evolution, motor activity of head, eyes, face, trunk, extremities, other complicating factors (cyanosis, trauma, emesis).

Postictal state: Incontinence, confusion/sleepy, headache, focal neurologic deficits, time to recovery of normal function (nearly immediate for syncope, minutes to hours for postictal, but usually less than 24hours)?

Past medical history (predisposing factors): Chronic illnesses (endocrine, hepatic, neoplastic, renal), history of seizures, CVA, CNS infection, autoimmune disease, head trauma, medications.

Development: Appropriate for age?

Family history: Seizures, epilepsy, neurocutaneous syndromes, other neurologic disorders?

Social history: Risk of physical abuse? Drug/alcohol abuse?

Physical examination should note the following: General appearance (dysmorphic features, associated injury pattern, signs of infection), vital signs, growth and head circumference percentiles, head (trauma, VP shunt), eyes (pupils, papilledema, retinal hemorrhages, angiomatosis, pigmentation), ears (hemotympanum, otitis media), nose (CSF rhinorrhea), mouth (drooling indicates aspiration risk, tongue laceration is suggestive of a seizure), neck (injury, meningeal signs), lungs (aspiration pneumonia), heart (rhythm abnormalities, congenital heart disease), incontinence, extremities (injuries), and skin (trauma, neurocutaneous stigmata). Neurologic evaluation should include: time to recovery, retrograde amnesia, speech difficulty, cranial nerves function, herniation signs, posturing, postictal deficits such as Todd paralysis, sensory loss, pathological reflexes, coordination or gait changes

Diagnostic tests for seizures are usually low-yield without historical or exam findings to suggest possible abnormalities. Routine screening labs, depending on the setting, may include electrolytes, glucose, Ca and Mg. Hyponatremia and hypoglycemia can cause seizures, whereas hypocalcemia and magnesium abnormalities resulting in hypocalcemia may cause tetany which resembles seizures. If the patient is on chronic AEDs for seizure control, then obtaining blood levels provides valuable information regarding compliance, drug efficacy, and possible toxicity. CBC, BUN/Creatinine, liver function tests, and PT/PTT are particularly of low yield unless the clinical circumstances suggest a specific problem related to these. An ABG, CPK, potassium and bicarbonate may have some benefit if the seizure was prolonged (see chapter on status epilepticus) and if there is a risk of rhabdomyolysis. Drug screens may be considered based on the social history. Toxicology can be used to screen for cocaine, amphetamines, PCP, TCA (tricyclic antidepressants) as well as possible withdrawal from benzodiazepines, alcohol, and barbiturates. Other drugs in overdose may cause seizures such as antipsychotics, methylxanthines, INH, antihistamines, and narcotics. If brain hemorrhage or infection is suspected, a lumbar puncture is indicated once elevated intracranial pressure (ICP) has been ruled out by history, exam, and possibly an imaging study.

Structural imaging studies of the brain, computed tomography (CT) and/or magnetic resonance imaging (MRI), are typically indicated in afebrile seizures and non-simple febrile seizures of unclear etiology. An emergent CT scan may be indicated in the following situations: 1) signs of symptoms of elevated ICP, 2) focal seizure or persistent focal neurologic deficit, 3) seizures with head trauma, 4) status epilepticus of unclear etiology. The CT is appropriate for detection of intracranial vascular lesions, acute bleeding and certain tumors larger than 1 cm. The MRI has better resolution for smaller and isodense lesions (e.g., low-grade gliomas). MRI may also provide better images in some areas (e.g., posterior fossa) and for some lesion types (e.g., neuronal migration disorders, lesions of neurocutaneous syndromes, AVM). The trade-off with MRI is that it is typically more difficult to schedule acutely, they take more time to complete and they require deeper sedation levels for young children. 50% or more of neuroimaging studies may be normal in patients with epilepsy (5).

The electroencephalogram (EEG) is a crucial tool in the diagnosis of seizures. It consists of a systematic measurement of electric potentials emanating from the brain's cortical surface which are less than 1/100th that of cardiac voltage on ECG. Numerous channels are recorded simultaneously from standard electrode placements to map brain electrical activity. Potentially provocative maneuvers (procedures known to provoke seizure potentials) known as activation procedures, such as hyperventilation, photic stimulation (e.g., blinking lights), and spontaneous sleep induction and emergence are employed to increase the yield of positive EEG findings by helping to trigger seizure potentials during the study. Because epileptiform activity may be present only at brief intervals, only 50-60% of routine EEGs are positive even in patients with known epilepsy. Activation procedures increase this yield. Seizure activity on EEG does not always accompany a visible seizure clinically. In general, although normal EEGs have low utility because they may be falsely negative, positive findings can be very helpful in determining the presence and classification of epilepsy to help direct treatment.

There are a wide variety of positive EEG findings. The classic epileptiform EEG abnormality is the sharp spike or wave which may be focal or generalized. Generalized spiking is usually large and obvious, while focal spikes (especially temporal lobe spiking) may be smaller and more subtle to see. Focal spikes or waves may help define an epileptic syndrome (e.g., benign childhood epilepsy with centrotemporal spikes). Other generalized patterns may also be definitive such as the 3-per-second spike and slow waves of childhood absence epilepsy (petit mal). Other mixtures of signals may also display characteristically defined patterns such as the mixture of spikes and slow waves that are different in each hemisphere described as hypsarrhythmia which is typical of infantile spasms. Postictal slowing may suggest a previous epileptic event if similar changes are not seen in a preseizure EEG. After a diagnosis of epilepsy is made, follow-up EEGs may sometimes be helpful in assessing response to therapy.

The yield on an EEG is dependent on multiple factors. Increasing positive findings with provocative measures was discussed previously. False negative results can be associated with epileptogenic foci that are deep to the cerebral surface, discharges that are orthogonal to the cerebral surface, excessive muscular artifact, or simply due to limitations in monitoring duration in comparison with the frequency of epileptiform EEG activity. Although there may be a variety of other abnormal EEG findings, such as focal slow waves or asymmetries of signals, they are non-specific regarding a diagnosis of epilepsy and are more useful in providing general information about cerebral function, encephalopathies, focal lesions, etc.

Epileptic seizure classifications by EEG are generally as follows: Partial simple seizures display spikes in a localized portion of the brain. Partial complex seizures display small spikes, usually in the temporal lobes. Partial seizures with secondary generalization demonstrates focal spikes progressing to generalized spiking. Generalized absence seizures display a 3 per second spike and slow wave pattern which is often precipitated by hyperventilation. Generalized tonic-clonic seizures display generalized spiking (photic stimulation may be a useful activation procedure). Infantile spasms, sometimes seen in severe developmental brain anomalies and tuberous sclerosis, display a hypsarrhythmia pattern (disorganized mixture of spikes and slow waves, different in each hemisphere). Benign epilepsy of childhood (Rolandic seizures) displays centrotemporal spikes or sharp waves ("Rolandic discharges") against a normal background. The Lennox-Gastaut syndrome displays slow spike and waves on an abnormal slow background.

Therapy for the acutely seizing patient is described in the chapter on status epilepticus. The decisions on whether to start chronic anti-epileptic drug (AED) therapy involves weighing risks and benefits of therapy with an in-depth discussion with the patient and family. If a seizure occurs secondary to an acutely reversible provoking factor (e.g., fever, hyponatremia, hypoglycemia, benzodiazepine withdrawal, post-impact, etc.), the treatment is directed toward the underlying cause. Short-term anti-seizure medication is used as needed, but no long-term anticonvulsant medication is typically employed.

Chronic therapy with AEDs should be started for seizures associated with any known structural lesion (e.g., brain tumor, AVM, intracranial bleeding, or infection such as HSV encephalitis). If there is no known underlying pathology, chronic AED therapy is also indicated for seizures associated with: 1) A family history of epilepsy in siblings (but not if in parents), 2) EEG with definite epileptic pattern, 3) History of prior acute unprovoked seizure(s), 4) Status epilepticus at onset, or 5) Remote history of head trauma, stroke, CNS infection, or static encephalopathy from birth with mental retardation or cerebral palsy. All of these factors suggest a higher risk of recurrence. The decision to start chronic AED therapy is less clear if there is a first-time unprovoked seizure without the above risk

factors. The risk for a second seizure in five-years is approximately 30% whereas it is approximately 46-73% for a seizure with any one of the above risk factors (7). The risks/costs of treatment include the side-effect profile of the intended AED, financial cost, impact of implementation on daily routine, and the chance that even with good compliance, the medication may not definitively prevent a seizure recurrence. For example, if a child's first seizure occurs at age 6 years, it is difficult to predict whether the next seizure will occur, tomorrow, next year, in another 6 years, or never at all. It is not beneficial for children to take daily medication for years to prevent an incident that may not be destined to occur during that time period.

The benefits of treatment include reducing the risk of recurrent seizures and their potential consequences such as associated injury, effects on self-esteem, and numerous restrictions such as loss of driving license privileges. In general, AED therapy is not indicated for the child who experiences a brief first seizure if the history confirms that the episode is truly an initial event, there is no family history of epilepsy, the neurologic examination is normal, and the EEG does not confirm a specific epileptic syndrome. The patient must be educated about the risk of subsequent seizures and should be advised about state driving regulations (8).

The initial selection of AED is typically based on seizure type. Carbamazepine (Tegretol) and phenytoin (Dilantin) are considered the initial medications to consider in all partial seizures and in generalized tonic-clonic seizures (with the exception of infants). Infants are usually treated with phenobarbital, since this drug is less toxic and the other drugs have some unattractive characteristics in infants such as poor GI absorption, poor oral formulations, etc. Generalized absence seizures are treated with ethosuximide (Zarontin). Valproic acid (Depakene, Depakote) may be effective both for partial and generalized seizures including absence seizures, but it is typically used only if initial therapy is not successful due to its side-effect profile. Oral benzodiazepines are also used as AEDs in some instances, usually in combination with other AEDs. Other newer AEDs cleared by the FDA since 1993 include felbamate, gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, zonisamide (9). The reader is referred to the reference list for further information on these medications and therapy for other epileptic syndromes. Approximately 80% of all persons with primary generalized seizure epilepsy and 65% of patients with partial seizure epilepsy achieve satisfactory control of seizures with AED therapy (10). The indications, pharmacology, and adverse effects of carbamazepine, phenytoin, phenobarbital, and valproic acid will be discussed briefly:

Carbamazepine is a first-line AED for the treatment of simple partial, complex partial, and general tonic-clonic seizures. The mechanism of action of carbamazepine is thought to be through use-dependent blockade of voltage sensitive sodium channels which results in stabilization of neuronal membranes and inhibition of repetitive firing of neurons. It may be orally or rectally absorbed, has a half-life of 12 to 17 hours and is extensively metabolized in the liver via the cytochrome P450 system. Dose-related side effects of carbamazepine include vertigo, ataxia, diplopia, and drowsiness. Approximately 4% of people treated with carbamazepine develop dermatologic reactions including erythematous and pruritic rashes, toxic epidermal necrolysis, erythema multiforme and Stevens-Johnson syndrome. The onset is usually within the first month of treatment but can be delayed up to 6 months. Serious blood dyscrasias, such as aplastic anemia and agranulocytosis have been reported, and although rare, occur at a frequency 5 to 8 times higher than that of the general population (11).

Phenytoin is used for the treatment of simple partial, complex partial, and generalized tonic-clonic seizures. The mechanism of action is similar to carbamazepine by use-dependent blockade of voltage-sensitive sodium channels. Phenytoin may be administered orally or intravenously. Because intravenous infusion rates of phenytoin are limited due to associated cardiac side-effects, fosphenytoin (an ester of phenytoin which is cleaved to phenytoin in the body) is commonly used for emergent loading (refer to the status epilepticus chapter). Phenytoin is metabolized in the liver in a concentration dependent, non-linear fashion. As a result, the half-life and time to steady state are dose dependent. Dose related side effects include nystagmus, ataxia, sedation, mental status changes, ophthalmoplegia and increased seizure frequency. Cosmetic side effects, including gingival hyperplasia, hirsutism and acne, are commonly seen and can be barriers to compliance in adolescent patients. A rash is the most common idiosyncratic reaction seen in 5-10% of people treated with phenytoin. It is typically morbilliform, may be accompanied by fever, and usually occurs in the first 3 months of treatment. Serious side effects such as agranulocytosis, aplastic anemia, hepatitis, and nephritis are rare (11).

Phenobarbital is frequently used in the treatment of neonatal seizures (see chapter on neonatal seizures) and seizures that occur in the first year of life. It is effective for both generalized tonic-clonic seizures, and partial seizures at all ages, but unfavorable cognitive side effects and concerns about the potential for adverse effects on the developing brain limit its use. Phenobarbital acts by various mechanisms including potentiating inhibitory neurotransmission by increasing the duration of time that gamma-aminobutyric acid (GABA) mediated chloride channels remain open. It is absorbed enterally and can also be given intravenously or intramuscularly. Phenobarbital is metabolized in the liver by the cytochrome P450 system, and it can induce the rate of metabolism of itself and other drugs that are metabolized thought this system. The clearance of phenobarbital is slow, with a half-life of 1 to 5 days. The dose-related adverse effects of phenobarbital include sedation, slowed thinking and ataxia. In children, however, paradoxic irritability and hyperactivity are also common side effects. (11).

Valproic acid has a broad spectrum of AED activity which includes generalized seizures such as myoclonic, tonic, atonic, absence, generalized tonic-clonic seizures and partial onset seizures. The mechanism of action of valproic acid is not completely understood. It has several different actions in vitro which may contribute to its AED effect including enhanced GABA-mediated inhibition and blockage of voltage-activated sodium currents. Valproic acid is orally administered, hepatically eliminated, and has a half life of 8 to 9 hours. Dose-related adverse effects of valproic acid include tremor, sedation, fatigue, and ataxia. Valproic acid can produce local gastrointestinal irritation that can lead to abdominal pain, nausea, diarrhea, or pancreatitis. Potentially fatal hepatotoxicity has been observed, usually within the first 6 months of therapy, and typically in children under 2 years of age. Valproic acid should be used with caution in women of child bearing age due to its teratogenic effects and association with polycystic ovaries (11).

All of the above AEDs have extensive protein binding and are hepatically metabolized. As a result, their levels are significantly affected by conditions and other medications which may affect protein binding and hepatic enzyme function.

Reasons for failure to respond to single AED therapy include noncompliance, inadequate serum AED levels, incorrect classification of seizure type, and continued exposure to seizure precipitants. If AED therapy is changed, the transition should include a slow wean off the original AED. If two trials of AEDs as monotherapy are ineffective, the chances of obtaining seizure control with additional medication trials are less than 15% (5). Trials of combinations of AEDs with different mechanisms of action are is also an alternative although this increases the risk of drug-drug interactions. About 30% of all patients with epilepsy continue to have seizures that appear to be resistant to all pharmacologic manipulations (1,4).

Nonpharmacological therapies for seizure control are usually reserved for medically refractory cases of epilepsy. These modalities include epilepsy surgery, vagus nerve stimulation, and the ketogenic diet.

Epilepsy surgery may be considered for patients with medically refractory seizures that interfere significantly with their lifestyle. Medical refractoriness is not well defined, but it can generally begin to be considered when seizures continue despite adequate monotherapy trials of two AEDs. Patients with simple partial seizures alone are generally not considered for surgery because the risk is likely to exceed the benefit. However, patients with complex-partial seizures or generalized motor seizures occurring as infrequently as once every few months can be candidates if these sufficiently impede academic or job performance, driving, and employment opportunities (12). Epilepsy surgery is contraindicated in children with benign focal epilepsy of childhood, idiopathic generalized epilepsy, and progressive medical or neurologic disorders (12). Presurgical evaluation is focused upon delineation of the epileptogenic zone (the region of cortex capable of generating seizures). The evaluation includes clinical history, ictal and interictal video, EEG, possibly invasive EEG, neuroimaging (MRI, SPECT, PET, magnetic resonance spectroscopy), and neuropsychologic assessment. A recommendation for surgery is made when the epileptogenic zone has been adequately defined, and the proposed procedure is believed to be associated with a high likelihood of seizure relief and a low risk of neurologic and cognitive morbidity (12).

The types of surgery performed in patients for refractory epilepsy included corticectomy, lobectomy, lesionectomy, hemispherectomy, corpus callosotomy, multiple subpial transection, and newer procedures including gamma knife surgery and deep brain stimulation (11). Early consideration for surgery is important to capitalize on the plasticity of the developing brain and to minimize losing developmental and behavioral milestones.

Vagus nerve stimulation (VNS) is FDA approved for use as adjunctive therapy for adolescents over 12 years of age and adults whose partial-onset seizures are refractory to AEDs (1,5). These patients are also usually not epilepsy surgery candidates. The mechanism of action of VNS is uncertain. A generator is placed surgically and it delivers programmed electrical pulses which may help to interrupt seizures or reduce seizure severity. Patients who experience auras warning them of an impending seizure can stop or shorten the length of the seizure by activating the VNS.

The ketogenic diet is a high fat, low protein and low carbohydrate diet used to treat intractable epilepsy. It was originally developed in the 1920s at the Mayo Clinic and was widely used until the 1940s when more effective and easier to use AEDs were developed. The ketogenic diet is still used by some neurologists today; however mostly for children who endure multiple daily seizures. The diet places the body in a state of starvation which forces it to utilize more fat than usual for energy, which results in more ketone by-products (hence the name "ketogenic") which serve as an alternative energy source for the brain. The exact mechanism for the ketogenic diet's efficacy is unclear, and it is on the FDA list of "experimental treatments" (1).

Lifestyle factors can contribute to seizure control and attempts should be made to manage them while encouraging normal development. Some lifestyle modifications may include: 1) Taking chronic AED medications regularly. 2) Getting enough sleep, avoiding alcohol, drugs other interacting medications. 3) Emergency plan of access to medical care, medical condition identification bracelet, and possibly rectal diazepam to be used in an emergency for a prolonged seizure. 4) Ongoing monitoring of AED levels, side-effects, adequacy of seizure control. 5) Ongoing monitoring of development, school performance. 6) Water and fall precautions. 7) Restrictions, especially as they relate to a driver's license. 8) Maintaining previous normal activity and disciplinary measures as much as possible and avoiding over-protection.

About 60-70% of patients with newly diagnosed epilepsy enter long-term remission, usually on a single AED. Patients who remain seizure-free for several years may be considered for weaning off AED therapy. Factors affecting the decision to wean AEDs and when to do this depend primarily on the type of epilepsy syndrome present (e.g., benign epilepsy with centrotemporal spikes tends to be "outgrown" while a structural lesion such as a brain tumor or AVM may have a perpetually high risk of seizures despite good control). Other factors that favor successful withdrawal include: single type of seizure, normal neurologic examination, normal IQ, and normal EEG following treatment. The benefits of withdrawal (freedom from daily medication, reduction of side effects, decreased risk of teratogenic effects) must be balanced against an approximately 20-30% probability of seizure recurrence (with possible loss of job, injury, effects on self-esteem) (1). If the decision to discontinue AED therapy is made, the medication should be gradually weaned over weeks to months to avoid withdrawal seizures.

Short occasional seizures are not felt to be associated with additional brain injury of long-term significance. About 30% of patients with epilepsy continue to have seizures that appear to be resistant to all pharmacologic manipulations (7). The response to the first AED is the most powerful predictor of long-term prognosis. Presuming that the correct type of seizure was diagnosed and therapeutic levels of the correct AED are obtained, a patient may be considered to have refractory epilepsy if seizure control is not achieved after the first two to three AEDs used. These patients are usually treated with multiple AEDs, which in combination, may produce sedative and adverse behavioral effects. However, high seizure frequency, prolonged seizures, and episodes of status epilepticus can lead to cognitive decline. In some patients, excessive seizure activity may be associated with detrimental cerebral histologic changes such as dendritic sprouting, synaptic reorganization, glial proliferation, and cell death (7). Also associated with AED toxicity and/or excessive seizure activity are psychosocial dysfunction, poor academic achievement, diminished self-esteem, dependent behavior, and a restricted lifestyle.

In the case at the beginning of the chapter, a developmentally normal boy with no personal or family history of seizures has an acute event that is suggestive of a seizure given its abrupt onset and description, as well as the persisting focal neurologic deficit which gradually resolves (which is likely a Todd paralysis). The exam finding of a tongue laceration is also suggestive of a seizure. The transient left hemiplegia and hyperreflexia are consistent with a Todd paralysis. The elevation in blood glucose is postictal hyperglycemia. The CT was indicated due to persisting focal neurologic deficits in the patient although he did not have a history suggestive of trauma, infection, or focal structural lesions.

The patient is appropriately hospitalized for observation given his persisting neurologic deficit. The EEG confirms the diagnosis of benign Rolandic epilepsy with centrotemporal spikes, an idiopathic epileptic condition with characteristic EEG findings. Given this diagnosis and the fact that the patient experienced a first-time seizure, observation without AED therapy is reasonably employed. Although he has a recurrent seizure, he does well on carbamazepine. He is successfully weaned off therapy after adolescence which is consistent with the good prognosis of this particular epileptic syndrome.

Questions

1. List 4 basic types of seizures (hint: two are partial and two are generalized).
2. List some of the old names that correlate to each of the above 4 seizure types and indicate the reason these old names were used.
3. A 14 year old girl is found unconscious. Witnesses say that she had some facial twitching. She gradually awakens and tells you that she smelled some burning rubber just prior to feeling faint. She tried to call for help, but couldn't speak. She now seems to be normal. A CT scan demonstrates a left temporal lobe arteriovenous malformation. What seizure type is she likely to have had and why?
4. Can the term petit mal be used to describe a seizure of small jerking movements of one arm?
5. Name some tests/studies which would be ordered for a 7 year-old girl who presents to the emergency department actively having a generalized seizure which stops spontaneously. She is afebrile and was brought in by her babysitter who is unaware of any history except that she may have been on some kind of medicine.
6. Why would an eventual MRI be useful for the patient in questions 5 if there are no obvious reasons for the seizure?
7. If a patient has no epileptiform activity on an EEG does that rule-out epilepsy? Why?
8. What are typical EEG findings in generalized absence seizures? In infantile spasms?
9. What AEDs (anti-epileptic drugs) are used for treatment of generalized absence seizures?
10. What percent of children with epilepsy eventually enter long-term remission? What percent of children with epilepsy never become seizure free on AEDs?

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Answers to questions

1. Partial simple (also called "partial elementary" or "focal motor"), partial complex, generalized tonic-clonic, generalized absence.
2. Focal motor seizures (partial simple) because only one part of the body exhibits tonic clonic seizures. "Jacksonian seizures" describe focal motor seizures, while "Jacksonian march" describes a partial simple with secondary generalization because of gradual spread of motor activity. Temporal lobe epilepsy (partial complex) due to lesions in the temporal lobe. Psychomotor seizures (partial complex) because they display behavioral changes in addition to facial motor abnormalities, such as twitching and grimacing. Grand mal (generalized tonic-clonic) because they exhibit grand abnormalities as manifested by generalized jerking. Petit mal (generalized absence) because they exhibit smaller abnormalities limited to the eyes and face in most instances, and also because these patients are generally in elementary school and thus petit in size.
3. Partial complex seizures. She has experienced an aura (burning rubber smell). The witnesses suggest mostly facial motor symptoms. She lost consciousness. The temporary expressive aphasia suggests a temporal lobe origin which is confirmed on CT scan which identifies a lesion in the left temporal lobe (which is why this used to be called temporal lobe seizures). Students will often confuse this presentation with generalized absence seizures, which usually occurs in elementary school aged children who have just a few seconds of impaired/loss of consciousness. This is not a partial simple seizure because there are motor, aura, aphasia and olfactory symptoms, in addition to loss of consciousness.
4. No, petit mal refers to generalized absence seizures. Jerking of one arm (even if they are small jerks) are partial simple seizures (focal motor), not generalized absence (petit mal).
5. Electrolytes, glucose, toxicology, AED levels, CT of the head, lumbar puncture would be a basic set of initial tests. An eventual EEG would be in order if no obvious precipitating factors were found.
6. The MRI has better resolution for smaller and isodense lesions (e.g., low-grade gliomas). MRI may also provide better images in some areas (e.g., posterior fossa) and for some lesions types (e.g., neuronal migration disorders, lesions of the neurocutaneous syndromes, AVM).
7. No, a negative EEG does not rule out epilepsy. False negative results can be associated with epileptogenic foci that are deep to the cerebral surface, discharges that are orthogonal to the cerebral surface, excessive muscular artifact, and simply due to limitations in monitoring duration in comparison with the frequency of epileptiform EEG activity. Of all the seizure types, partial complex seizure foci are the most difficult to reliably identify on EEG.
8. Generalized absence seizures typically have a generalized 3 per second (Hertz) spike and slow wave EEG pattern, often provoked by hyperventilation. Infantile spasms have a hypsarrhythmia pattern on EEG which has an asymmetric disorganized mixture of spikes and slow waves.
9. Ethosuximide and valproic acid are used to treat generalized absence seizures.
10. 60-70% of children with epilepsy eventually have good seizure control on AEDs and enter into long-term remission, but 30% will never become seizure free on AEDs.

Chapter XVIII.5. Status Epilepticus

Loren G. Yamamoto, MD, MPH, MBA

A 6 year old male is noted by his mother to have a generalized tonic clonic seizure. He is unresponsive and his eyes are rolled up. She tries to blow on his face and shake his shoulders, but the seizure continues. His face is turning blue so she calls 911. The sequence of events proceeds as below:

Time 0: Onset of seizure.
Time 3 minutes: Mom calls 911 (activating EMS).
Time 12 minutes: Ambulance arrives at home.
Time 14 minutes: Ambulance crew at the patient's side. Oxygen saturation 80%. Patient still seizing.
Time 20 minutes: Mask ventilation with oxygen, IV started. Oxygen saturation improves to 95%.
Time 25 minutes: Lorazepam 0.1 mg/kg IV given. Patient being transported, treatment en route. Oxygen saturation is now 100%.
Time 31 minutes: Patient arrives in the emergency department, still seizing.
Time 33 minutes: Lorazepam 0.1 mg/kg IV repeated.
Time 34 minutes: Phenytoin or fosphenytoin 10 minute infusion started (larger patients may require longer infusion times).
Time 44 minutes: Patient still seizing so another anticonvulsant such as phenobarbital is administered.
Time 54 minutes: Seizures continue.

Status epilepticus is defined as prolonged seizures which continue or occur in rapid succession with relatively brief intervals in between. A minimum time duration is not part of a universal definition. The most severe form of SE is generalized tonic clonic SE which results in respiratory compromise (hypoxemia and hypercapnia), with hypermetabolic cerebral activity (excessive cerebral oxygen demand). This results in respiratory and metabolic acidosis. Skeletal muscle contraction may result in rhabdomyolysis and hyperkalemia. Other forms of status epilepticus may not be as obvious. Partial complex SE and absence (petit mal) SE, are less common and may be difficult to recognize. The discussion in this chapter will focus on generalized tonic clinic status epilepticus.

Status epilepticus may be due to several causes. Patients with epilepsy or brain anomalies may present with SE, or they may have breakthrough seizures presenting with SE. SE can also result from periods of anticonvulsant non-compliance. SE may be due to encephalitis or other brain infections. SE may be due to drug overdose toxicity (e.g., isoniazid), traumatic brain injury, neoplastic conditions, metabolic derangements, encephalopathy or cerebrovascular accident.

The desired goal in the management of status epilepticus is to terminate the seizures and restore the patient to baseline as soon as possible while maintaining oxygenation, circulation and normoglycemia (1). Prognosis is determined by the etiology and the duration of SE (1). Complications of prolonged SE include hypoxic ischemic brain injury which may be due to the combined factors of prolonged hypoxia, hypermetabolic cerebral oxygen demand, and respiratory acidosis.

In addition to terminating the seizures, treatment for possible treatable causes of SE should be initiated. Acyclovir and ceftriaxone are commonly administered while treating SE, since the etiology of SE may not be determined until much later.

Since benzodiazepines have the most rapid anticonvulsant onset, it is well accepted that the initial drug to treat SE should be a benzodiazepine. Phenytoin and barbiturates can also be used IV, but their onset time is slower. Other IV drugs such as lidocaine and magnesium have been reported to have anticonvulsant activity, but their use in SE is not routine. Paraldehyde is difficult to use and is no longer pharmacologically available in the United States (2). Reports of propofol and inhaled anesthetics having efficacy in SE have been cited elsewhere (1,2). IV valproic acid has been suggested as an additional agent (3).

IV lorazepam (Ativan) is the most commonly recommended benzodiazepine for SE, because of its longer duration. Diazepam (Valium), which can be given IV or rectally, is also very effective. Midazolam (Versed) can also be used, with its main advantage being that it can be given IM, while the IM route is not recommended for lorazepam and diazepam. If the patient has an IV, lorazepam should be given (diazepam can be used if lorazepam is not available). If an IV is not available, then rectal diazepam or IM midazolam can be used. If rectal diazepam is used, its dose should be doubled or quadrupled in order to get the same effect as the IV dose. A commercially available unit dose rectal diazepam (Diastat) is available or one could administer the IV form of diazepam by: 1) For small doses, a 1cc syringe could be used with lubricant applied to the syringe itself. Then the barrel of the syringe can be directly inserted into the rectum. 2) For larger doses, the diazepam can be drawn into a larger syringe and a rubber catheter or feeding tube can be attached to the hub with the other end inserted into the rectum. The diazepam is pushed through the tube or catheter, followed by an air bubble to clear the tube.

SE is often treated in a stepwise approach with an anticonvulsant drug given every 5 to 10 minutes until SE terminates. A benzodiazepine is administered first (e.g., lorazepam 0.1 mg/kg). This can be repeated in 5 to 10 minutes, if SE continues. In most instances, in patients who were not previously on chronic anticonvulsants, IV loading with one of the phenytoins (phenytoin or fosphenytoin) should immediately follow the first benzodiazepine dose without waiting to see if the benzodiazepine will work. Infants, and especially neonates, may be an exception where phenobarbital may be preferred (1) . For epilepsy patients who are already on anticonvulsants, stat drug levels should be obtained to determine if these are within the therapeutic range. If they are not, an IV or oral dose (or via nasogastric tube) can be given to raise their level appropriately.

In many instances, this first or second benzodiazepine dose will terminate SE and restore the patient to their baseline state (1). These cases are relatively simple and are at less risk for complications. For the purpose of this discussion, this chapter will refer to this as simple status epilepticus. It should be expected that once the benzodiazepine wears off, seizures may recur unless a longer acting anticonvulsant has been administered or a subtherapeutic anticonvulsant level has been brought back up into the therapeutic range.

When the first one or two doses of a benzodiazepine fail to terminate SE, these patients are at higher risk for prolonged SE and complications secondary to this. Refractory status epilepticus can be loosely defined as SE which continues despite an initial anticonvulsant drug regimen (such as a benzodiazepine and phenytoin). If SE continues after two doses of a benzodiazepine, refractory SE should be anticipated. The treatment of refractory SE is more complex and controversial.

The case described in the beginning of the chapter indicates a typical sequence of drugs administered in an attempt to terminate status epilepticus. This sequence may seem fast or slow to you depending on your perspective. It is actually fast since these times are highly ideal and medications are given rapidly without hesitation or pause for prehospital communication. In most instances when conditions are less than ideal, it is common for one hour to elapse while initial anticonvulsant agents are still being administered. One published sequence which completes its second line of drugs within 30 minutes is deceivingly fast because "time 0" is when treatment (ABC+vascular access and glucose) is initiated and only 5 minutes is given to complete an IV benzodiazepine, IV glucose, IV phenytoin

(published recommended infusion times for this drug alone are longer than 5 minutes), brief history and neuro exam, reassessment of vital signs, a check of anticonvulsant levels and a repeat phenytoin mini bolus (all between Time=10 minutes to Time=15 minutes) (1).

Another published sequence defines its "time 0" when the first benzodiazepine is administered IV (this equates to Time=25 minutes in the sequence described in the case). This sequence uses two doses of a phenytoin and two doses of phenobarbital to end at approximately 68 minutes from the time that the first benzodiazepine was administered (4) (add about 25 minutes to this for the total duration of SE).

Neither of these published sequences provides for a period of observation following the administration of an anticonvulsant to see if the drug is successful in terminating SE. This is a common practice and it adds to these time sequences which already approach or exceed one hour. One source states that "the treating physician should allow adequate time for the anticonvulsants to reach therapeutic levels in the brain" (5). A major problem with this approach is that the "wait and see" time periods add up rapidly if SE is not terminated. This time is frequently further prolonged by delays in obtaining IV access, longer prehospital transport times, medication administration delays and if smaller initial doses of benzodiazepines are initially used (e.g. 0.05 mg/kg of lorazepam). No agent or combination of agents is universally reliable in terminating SE (1). It is easy to see how SE can sometimes continue for 2 or 3 hours before it is finally terminated. This is not ideal.

Since it is best to minimize the time of SE, it is best to minimize the time in which anticonvulsants are administered (1). Because of this, it may be unwise to give small doses and wait between anticonvulsants to see if it works (1). Larger full loading doses of anticonvulsants should be preferred. The onset time pharmacology of these drugs may have to be ignored (onset times range from 2 to 30 minutes) in order to minimize the duration of the anticonvulsant sequence. This "wait and see" approach should be modified to a "give, look and give another" approach when managing refractory SE. Refractory SE can be suspected early (as opposed to simple SE) when the first two doses of a benzodiazepine fail to terminate SE.

In the pharmacologic management of refractory SE, there are three basic approaches: 1) the "wait and see" approach, 2) the "give, look and give" approach, 3) the early rapid sequence intubation approach. While the first approach ("wait and see") is commonly used, this practice should be discouraged in managing refractory SE; thus, it should be eliminated from consideration in order to minimize the duration of refractory SE as discussed above. This leaves only two reasonable approaches.

In the early rapid sequence intubation (RSI) approach, refractory SE is recognized early once failure to respond to the first two large doses of benzodiazepines and the phenytoin load is noted. RSI (intubation facilitated by pharmacologic paralysis and deep sedation) has been discussed elsewhere and is beyond the scope of this chapter (6). Early RSI will paralyze the patient to optimize oxygenation, restore ventilation (reversing respiratory acidosis) and halt skeletal muscle contractions (halting rhabdomyolysis and excessive peripheral oxygen consumption). Its commonly recognized disadvantage is that continued seizure activity cannot be determined without the use of continuous electroencephalography (EEG) which is not available in most centers (7). However, the treatment for continued seizures is more anticonvulsants. RSI is often accompanied by a potent anticonvulsant and cerebroprotective agent such as thiopental. Etomidate is often used as a sedative in RSI, but this agent may worsen a seizure condition or cause myoclonus (8). RSI facilitates the administration of maximal anticonvulsant therapy since there is no risk of respiratory depression (the patient is already paralyzed and intubated). Loading with maximal doses of IV phenytoin and phenobarbital can now take place. Although the patient is paralyzed and continued seizure activity cannot be recognized, maximal doses of a benzodiazepine, phenytoin and phenobarbital have been administered. What more could be done even if the clinician could still see the seizures? Adding barbiturate coma, a high dose benzodiazepine infusion, propofol or IV valproic acid could be considered (1,2,3). Short acting paralyzing agents allow reasonably prompt recovery to regain the ability to witness continued seizure activity (4). General anesthesia with barbiturate coma with paralysis is commonly recommended for SE exceeding 60 minutes (5), yet the decision to initiate RSI (a similar procedure) a few minutes earlier, is paradoxically frowned upon by some. Refractory SE durations approaching and exceeding an hour are not uncommon. Since neuronal damage may occur long before 60 minutes of seizures (5) and barbiturate coma may be time consuming to initiate, RSI performed earlier may provide its benefits early and facilitate the rapid initiation of barbiturate coma if it is required. RSI also facilitates expedient neuroimaging which is frequently necessary in SE patients. Several reports recommend endotracheal intubation in the management sequence of refractory SE (1,5,9). If this is so, then should intubation be performed early versus late?; without RSI versus with RSI? These preferences determine if one will be an advocate of an early RSI approach.

The "give, look and give" approach is also a reasonable approach for those who judge the disadvantages of early RSI to outweigh its advantages. Continued seizures after the first two large doses of a benzodiazepine and the phenytoin load should signify refractory SE and a high risk patient. There is a high risk of apnea when phenobarbital is given in combination with benzodiazepines, thus intubation may be necessary (1). Barbiturate coma, benzodiazepine infusion, propofol, IV valproic acid (1,2,3) and/or rapid sequence intubation (if not already done) can be considered after this point.

The table below describes a typical time sequence difference between the "Give look and give" approach compared to the "Early RSI" approach. The comparison starts at time=20 minutes when paramedics or medical personnel first arrive.

Time	"Give look and give" approach	"Early RSI" approach
20 min.	Oxygen + p.r.n. mask ventilation.	Oxygen + p.r.n. mask ventilation.
25 min.	Lorazepam 0.1mg/kg IV.	Lorazepam 0.1mg/kg IV.
27 min.	Phenytoin 15-20mg/kg IV over 10 min.	Phenytoin 15-20mg/kg IV over 10 min.
37 min.	Lorazepam 0.1mg/kg IV.	Lorazepam 0.1mg/kg IV.
42 min.	Phenobarbital 15mg/kg IV slowly.	RSI drug sequence begins.
46 min.	Visible seizures continue.	Visible seizures stop. Patient intubated.
47 min.	Phenobarbital infusion continues.	Phenobarbital 25 mg/kg IV.
50 min.	Visible seizures continue.	Phenobarbital infusion complete.
52 min.	Phenobarbital infusion complete.	
53 min.	Apnea develops.	
55 min.	Intubation done under difficult conditions.	
60 min.	Additional phenobarbital 10mg/kg IV.	

In refractory SE, when maximal anticonvulsant administration may be required, the early RSI approach completes drug administration faster and intubation is facilitated. Additionally, the patient is paralyzed and intubated earlier facilitating oxygenation and

halting skeletal muscle activity. Phenobarbital must be given slowly following a benzodiazepine to prevent apnea, but this often happens anyway. The time sequence can be shortened by using fosphenytoin which can be given IV faster than phenytoin, or interrupting the phenytoin infusion to give the second lorazepam dose.

In summary, to minimize the duration of SE, the "wait and see" approach should be discouraged in favor of the "give look and give" approach or the early rapid sequence intubation approach in order to minimize the duration of drug administration and the duration of SE. Refractory SE risk should be recognized earlier (when SE continues despite the first two benzodiazepine doses), so that anticonvulsant administration can be done more aggressively since time is critical.

Questions

1. After oxygen, the first drug that is administered to a patient in status epilepticus is from what drug class?
2. Name three other anticonvulsant drugs, not belonging to the class above, that can be given IV?
3. Name two ways that diazepam can be given in status epilepticus?
4. Which benzodiazepine has the longest duration?
5. In status epilepticus, what drug should be administered after a benzodiazepine in most instances (other than in neonates)?
6. What is the most serious complication of status epilepticus?
7. Name 5 causes of status epilepticus?

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Answers to questions

1. Benzodiazepines.
2. Phenytoin (or fosphenytoin), phenobarbital, valproic acid.
3. IV and rectal.
4. Lorazepam.
5. Phenytoin (or fosphenytoin).
6. Hypoxic ischemic brain injury, death.
7. Epilepsy, encephalitis, neoplasm, drug overdose, metabolic derangement, cerebrovascular accident, trauma, etc.

Chapter XVIII.6. Infant Botulism
Daniel W. Ulrich, MD

This is a 3 month old male who presents to the pediatrician's office with a chief complaint of decreased activity, poor feeding and constipation. Pertinent past medical history reveals that the infant was born at 39 weeks gestation, with no complications during the pregnancy or birth. The infant is exclusively breast fed, up to date on immunizations and has suffered from no previous illness. On further questioning, his mother reports her son has not been himself for the past week. He has had no fever and there are no sick contacts. He has been less active, with a weak cry during this time. His mother also notes the infant has not been as interested in feeding and has suffered from constipation. His urine output is decreased with only four wet diapers in the last 24 hours. Typically, he has 3-4 soft stools per day, usually after feeds, but has had no bowel movement in the past 5 days.

Exam: VS 37.0, P 114, R 22, BP 98/62, Wt. 5.3 kg (75%), Ht. 57cm (50%). He is awake, non-toxic appearing, with expressionless facies and a weak cry. His anterior fontanel is flat and soft. He has poor head control. He has diminished pupillary reflexes, absent corneal reflexes, bilateral ptosis, and decreased tearing. He has a weak suck and gag reflexes with increased oral secretions. His neck is supple without adenopathy. Heart and lungs are normal. Aeration is good. His abdomen is soft, full, non-tender, with decreased bowel sounds throughout. No hepatosplenomegaly. Rectal exam shows no stool in the rectal vault and decreased anal sphincter tone. His extremities are slightly cool, with delayed capillary refill. His skin shows no rash or petechiae. He has decreased muscle tone throughout and diminished deep tendon reflexes.

He is hospitalized for possible infant botulism. A sepsis work up is done and he is started on IV fluids and empiric antibiotics for sepsis. Stool samples are sent for Clostridium botulinum toxin assays. His cultures are subsequently negative. His clinical condition worsens such that he cannot feed and he eventually develops hypoventilation and respiratory insufficiency requiring mechanical ventilation. An electromyography study is done which shows brief, small, abundant, motor unit potentials, known by the acronym BSAP, a characteristic pattern associated with infant botulism (1). He gradually improves and he is weaned off the ventilator after 8 days. His stool assay returns positive for botulism toxin. He continues to gradually improve over the next three weeks such that he is able to feed on his own and he is then discharged from the hospital.

Clostridium botulinum is a gram negative, spore forming obligate anaerobe whose natural habitat worldwide is soil, dust, and marine sediments. It is found in a wide variety of fresh and cooked agricultural products including fruits, vegetables and honey (2). Due to a number of cases being linked to ingestion of honey in infants (honey is often used to treat constipation), it is recommended that no infant be given honey under 1 year of age (2,3,4). However, it should be noted that the source of clostridium spores is often not conclusively proven in most cases, with environmental exposure to spores in dirt or soil often thought to be a more likely exposure route (associated with a parent who works in construction or earth moving occupation).

The usual incubation period is estimated at 3 to 30 days from time of exposure to spores (2). Infant botulism has been reported from all inhabited continents except Africa. Notably, the infant is often the only ill family member. The most striking epidemiological feature of infant botulism is its age distribution, in which 95% of cases are found between the ages of 3 weeks to 6 months of age, with a peak between 2-4 months of age (2). Ingested spores of C. botulinum germinate, colonize the infant colon, and slowly produce neurotoxin within the GI tract. The toxin is subsequently absorbed and carried by the blood stream to peripheral cholinergic synapses, in particular the neuromuscular junction, where it binds irreversibly (3). The neurotoxin action results in a flaccid paralysis and hypotonia, with the autonomic nervous system less severely affected. Function is regained only when new motor endplates are regenerated which can take weeks to months (1).

The clinical spectrum of infant botulism ranges from mild disease to sudden infant death. The onset can be insidious or fulminant. The disease typically manifests as a descending flaccid paralysis of the cranial nerve musculature with ptosis, blurred vision, diplopia, dysphagia, dysarthria and decreased gag and corneal reflexes. In fact, it has been stated that it is not possible to have botulism without having multiple bulbar palsies (5). However, in infants, symptoms of poor feeding, weak suck, feeble cry and even obstructive apnea (from a floppy tongue) are not often initially recognized as bulbar in origin (5). The classic picture of infant botulism is an initial presentation of constipation (defined as 3 or more days without defecation in a previously regular infant), listlessness, and poor feeding together with maternal breast engorgement. The typical patient often has an expressionless face, feeble cry, ptosis, poor head control, generalized weakness and hypotonia. Patients are most often afebrile unless a secondary infection is present and most initial laboratory tests are normal. The differential diagnosis includes sepsis (the most common admitting diagnosis), dehydration, constipation, hypothyroidism, other neurologic disease, inborn errors of metabolism or poisoning (5). The diagnosis is best confirmed with isolation of C. botulinum organism in the stool (often detectable only in the early stages of disease) or C. botulinum toxin in serum or stool. The toxin can be identified in the stool of infected infants for as long as 4 months (4), which explains why the clinical course can last for a few weeks for a few months. Although the electromyographic findings in infant botulism are unique, the procedure is painful and generally unnecessary unless the diagnosis is in question.

Treatment of infant botulism is fundamentally supportive and depends on the anticipation and avoidance of potentially fatal complications. Antibiotics should not be used routinely and should only be used to treat secondary infections (pneumonia, urinary tract infections, otitis media), because their use may result in the lysis of intraintestinal C. botulinum with liberation of additional neurotoxin (3). Of note, aminoglycoside antibiotics, which are weak pharmacologic neuromuscular blocking agents, should be particularly avoided since they will worsen paralysis acutely, often precipitating an acute respiratory arrest in unsuspected infant botulism patients initially being treated for sepsis (3,5). Human botulinum immunoglobulin (BIG), which acts by interrupting the neuromuscular blockade, has been approved for the treatment of infant botulism. A single intravenous dose of BIG has been shown to reduce the typical course of hospitalization from 5.5 to 2.5 weeks with a two-thirds reduction in the rate of intubation/mechanical ventilation (4).

Most infants will show gradual improvement over a period of 10 days to 2 months with rare cases of relapse. Common complications including respiratory failure (requiring mechanical ventilation), secondary infections (e.g., pneumonia and UTI) and SIADH require appropriate management to optimize the infant's ultimate prognosis, which is potentially excellent with a full neurologic recovery.

"Infant botulism" differs from "botulism" in that food-borne botulism results from the ingestion of a food in which C. botulinum has produced pre-formed toxin so its onset is more rapid compared to infant botulism. It is most commonly seen in older children and adults and often occurs in outbreaks traced to spoiled, low acidity canned foods (2). While all forms of botulism produce disease through a similar pathway, food-borne botulism more often begins acutely with gastrointestinal symptoms such as nausea, vomiting and diarrhea. A characteristic pattern of dysarthria, dysphagia, dry mouth, diplopia, and blurred vision with ptosis evolves during the onset of disease.

Fulminate and extensive paralysis, respiratory distress and apnea are more likely to be experienced with food-borne botulism. Wound botulism is an exceptionally rare disease, but is important to pediatrics because adolescents and children are disproportionately affected.

Questions

1. The mother of a 4 month old infant asks if it is okay to coat a pacifier with honey to soothe her baby, what is your response?
2. What is the basic mechanism of action of botulinum toxin?
3. Describe the typical clinical presentation of infant botulism. Why may the diagnosis be unclear initially? What is the classic age distribution?
4. What are the principle methods that can be used to confirm infection by C. botulinum?
5. What are the indications for antibiotic treatment in an infant with infant botulism? Why are aminoglycoside antibiotics contraindicated?
6. What is the role of human botulinum immunoglobulin in the treatment of infant botulism?
7. What is the prognosis for an infant infected with infant botulism?
8. Describe the basic difference between "botulism" and "infant botulism".

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Answers to questions

1. It is recommended to not give honey to any infant under 12 months of age.
2. Botulinum toxin is released by bacteria within the infant's GI tract. From here, the toxin is absorbed and carried by the blood stream to peripheral cholinergic receptors where it binds irreversibly. Clinically, the most important of the peripheral cholinergic receptors is the neuromuscular junction. Here the toxin's action results in flaccid paralysis and hypotonia, which are the classic clinical signs of infant botulism.
3. Initially, infected infants often present with a history of poor feeding, decreased activity and constipation. The diagnosis may not be considered initially because signs of an evolving bulbar palsy, flaccid paralysis and hypotonia may be subtle. Additionally, the infant may be worked up for sepsis if he appears toxic or "lethargic", or for constipation until the "classic" manifestations of infant botulism become apparent. The classic age distribution for infant botulism is 3 weeks to 6 months of age.
4. Isolation of the clostridium botulinum organism in stool can be accomplished in the early stages of disease, it is rarely isolated in blood. The most common method for proving infection is to isolate botulinum toxin in blood or stool samples. Toxin can be detected in the stool of infected infants for up to 4 months. Electrophysiological testing, specifically electromyography, can aid in ruling out other neurologic disorders such as Guillain-Barre syndrome, congenital myopathies, and myasthenic conditions.
5. The use of antibiotics in infant botulism should be reserved only for proven secondary infections such as pneumonia, otitis media or urinary tract infections. Aminoglycosides should be avoided as they are weak pharmacologic neuromuscular blocking agents which may potentate paralysis acutely or cause respiratory failure in an unsuspected infant with botulism being treated for sepsis.
6. Human botulinum immunoglobulin (BIG), which acts by interrupting the blockade of nerve receptors by botulinum toxin, has been shown to reduce the need for mechanical ventilatory support and shorten overall duration of hospitalization.
7. If recognized early and given appropriate supportive care minimizing complications, full recovery and a normal neurologic function can be expected.
8. Classic "botulism" is a food born disease in which high levels of toxin can be ingested in spoiled food. It often occurs in outbreaks linked to a particular source, and typically afflicts older children and adults. Wound botulism is rare, but is seen disproportionately in adolescents and children. Infant botulism has a more gradual onset. All types of botulism produce disease through a similar pathogenesis.

Chapter XVIII.7. Guillain-Barre Syndrome
Judy T. Okimura, MD

A 12 year old Caucasian female presents to the emergency room with a chief complaint of leg weakness. One week prior, she had a fever of 101.4 with vomiting and diarrhea. After 3 days, the vomiting and diarrhea resolved. She was doing well until this morning when she fell while trying to get out of bed and could not stand or walk without support. She has no headache, blurred vision, tinnitus, vertigo, dysphagia, or incontinence. There is no history of toxic ingestion. Her immunizations are up to date. While in the ER she complains that her arms feel weak.

Exam: VS T 37.0, P 84, R 24, BP 102/64. Height and weight are at the 25th percentile. She is alert, slightly tearful but cooperative. HEENT: She has no nystagmus and no papilledema. Her extraocular movements are intact. Pupils are equal and reactive to light. No facial weakness or asymmetry is present. Heart, lung and abdomen exams are normal. Neuro: Strength 4/5 in the upper extremities, 3/5 in the lower extremities. DTRs 1-2+ in the upper extremities and absent in the lower extremities. Sensation is intact in all extremities. Cerebellar function is normal except for the weakness. No cranial nerve abnormalities are noted. She refuses to walk.

CBC, electrolytes, BUN, creatinine, glucose, calcium and liver function tests are normal. Urine toxicology screen is negative. A lumbar puncture is performed. Opening pressure is normal. CSF analysis shows protein 146 mg/dL (high), glucose 70 mg/dL, 5 WBC per cu-mm, 1 RBC per cu-mm, and gram stain shows no WBCs and no organisms.

She is hospitalized for further management with a tentative diagnosis of Guillain-Barre syndrome. An MRI of the brain and spinal cord is normal. She is started on IVIG and over the next few days, she slowly regains strength in her arms and legs. However, she still requires assistance with walking at the time of discharge. She is referred to a rehabilitation hospital to continue outpatient physical therapy. She gradually improves over the next 5 months and eventually returns to normal activity.

Guillain-Barre syndrome (GBS) is an acute demyelinating polyneuropathy of the peripheral nervous system characterized by progressive flaccid paralysis (1). It is an acquired disorder that affects people of all ages, although only rarely in children under one year of age (2,3). It has a slight male predominance of 1.5 to 1 and has an estimated annual incidence rate of 1/100,000 (1,2).

The disease mainly affects motor nerves but can involve sensory nerves as well (3). Although typically presenting as a fairly symmetric ascending paralysis, GBS is now believed to be a heterogenous disorder with a wide range of clinical manifestations. It includes the classic demyelinating form, or acute inflammatory demyelinating polyneuropathy (AIDP), the axonal forms which include the acute motor axonal neuropathy (AMAN) and acute motor sensory axonal neuropathy (AMSAN), and clinical variants such as the Miller-Fisher Syndrome characterized by the triad of ataxia, areflexia, and ophthalmoplegia (4,5). AIDP is the most common subtype found in North America and Europe, while the axonal forms are more commonly seen in China (6).

Most cases in developed countries occur following an upper respiratory or diarrheal illness (1). Although the pathogenesis of the disorder remains unclear, GBS is suspected to cause an immune-mediated demyelination and axonal injury due to certain bacteria or viruses sharing antigenic sites with peripheral nerve myelin and/or axons (1,2). Campylobacter jejuni enteritis is the most commonly identified antecedent infection and is associated with more severe symptoms (4,6). Cytomegalovirus, Epstein-Barr virus, Mycoplasma pneumoniae, and Haemophilus influenzae have also been implicated in GBS (2,5).

Current research suggests that antiganglioside antibodies play an important role in the pathogenesis of GBS. Gangliosides are glycolipids containing sialic acid residues and are the surface components of many cells, including nerve cells. Many patients with GBS have antibodies to various gangliosides such as GM1, GD1a, GD1b, and GQ1b. Anti-GM1 antibodies are often found in classic GBS (AIDP), while anti-GQ1b antibodies are more commonly seen in the Miller-Fisher Syndrome (7). The outer membrane of Campylobacter's and other gram-negative bacteria is composed of lipopolysaccharides (LPS) which are complex glycolipids. The LPS of Campylobacter is unique in that it contains sialic acid and therefore resembles human glycoconjugates. It has been found to have antigenic molecules related to ganglioside GM1 and GQ1b (1,7). Through a process called molecular mimicry, antibodies against the C. jejuni LPS may crossreact with peripheral nerve myelin to cause demyelination (1).

Progressive weakness usually develops first in the lower extremities, then the trunk, upper extremities, and bulbar muscles. This pattern of ascending paralysis is fairly symmetric and develops gradually over a period of days or weeks. The child may develop an inability or refusal to walk and may later develop flaccid quadriplegia (3). However, 5-10% of children may initially have more weakness in the upper extremities, and some may have more proximal than distal muscle weakness (2).

Deep tendon reflexes are usually lost early in the course of the disease, although the proximal reflexes may still be present initially (2,3).

Sensory disturbance is also common and may occur in a glove-and-stocking distribution (8). Pain or paresthesias in the extremities, around the mouth, or on the back may be the presenting complaint in about 40% of patients. Pain in a band-like distribution may be present, and position and vibratory senses may be diminished (2). Muscle pain is also common initially in cases where there is an abrupt onset (3).

Approximately 50% of cases have bulbar involvement with the potential for respiratory insufficiency. Cranial nerve involvement may lead to facial weakness, difficulty swallowing, and problems with ocular motility. Dysphagia and facial weakness may herald respiratory failure requiring mechanical ventilation, a complication which occurs in 15-20% of patients (2,3). Autonomic dysfunction is uncommon but may present as arrhythmias and blood pressure instability including orthostatic hypotension (2).

The most common clinical variant of GBS is the Miller-Fisher syndrome with its triad of external ophthalmoplegia, ataxia, and areflexia. It is presumed to have a similar immune-mediated pathogenesis and pattern of recovery to classic GBS (1).

The cerebrospinal fluid (CSF) in affected patients is characterized by an elevated protein level without a WBC count elevation (i.e., normal cell counts) (3). This albuminocytologic dissociation is virtually diagnostic of GBS (1,3). About one-half of patients develop an elevated CSF protein during the first week of illness and most patients will show an elevation after the first several weeks of illness. The CSF protein peaks between 80 to 200 mg/dL. The CSF WBC count should not exceed 10 per cu-mm. A WBC count >50 per cu-mm or a predominance of segmented neutrophils should prompt the search for an alternative diagnosis such as meningitis, encephalitis, or transverse myelitis (2). The CSF glucose level should be normal and the culture negative.

Electrodiagnostic studies should be performed if there are atypical features, a rapid progression of illness, weakness that is severe or very mild, if there is delayed recovery, or if the diagnosis is unclear (2). Nerve conduction studies reveal slowing in both motor and sensory nerves (1,3). Electromyelography (EMG) may show acute denervation of muscle (2,3), but it does not show a primary myopathic process.

The differential diagnosis of GBS is large. A child with acute cerebellar ataxia may present with an acute gait disturbance and diminished tone. CSF pleocytosis is common and the protein level is usually normal (2). Spinal cord disease should be considered in a child presenting with acute lower extremity weakness, especially if there is a distinct spinal level of sensory loss, given the potential for irreversible cord injury by a compressive mass lesion (2). Transverse myelitis can present similarly, with back pain, a distinct sensory level, and rapidly progressive paralysis (2,8). Areflexia will be seen initially below the level of the lesion but hyperreflexia later develops. The CSF may show elevated protein, pleocytosis, and an increase in gamma globulin (8). MRI of the spinal cord should be obtained when the distinction is unclear. Poliomyelitis, now rare due to the routine immunization of children, can manifest as acute diffusely symmetric weakness, although it more commonly causes an asymmetric paralysis (2,8). Fever, meningeal signs, and muscle tenderness and spasm may also be present (8). It does not cause sensory disturbance and bowel and bladder function are almost never affected (2).

Myasthenia gravis may present with weakness which is often episodic and slowly progressive. There is almost always an associated ptosis or ophthalmoplegia, with preservation of sensation and reflexes (2). Botulism should be considered in a child less than 1 year of age presenting with weakness, a poor sucking reflex, weak cry, and constipation (8). Other common findings include swallowing difficulties and poorly responsive pupils. Older children will present with bulbar symptoms and weakness. CSF results will be normal and EMG reveals brief small abundant potentials which are diagnostic (8). Other causes of acute polyneuropathy include heavy metal intoxication, glue sniffing, tick paralysis, porphyria, SLE, and other collagen vascular diseases (2).

GBS is generally self-limited in children and full recovery can usually be expected (9). However, because of the potential for respiratory failure requiring mechanical ventilation, forced vital capacity, negative inspiratory force, and vital signs should be measured every 6 hours early in the course of illness to establish a trend. Rapidly decreasing vital capacity, dyspnea or fatigue, and deterioration of arterial blood gas values are indications for intubation and mechanical ventilation. Patients with dysphagia, shoulder weakness, or cardiovascular instability may also require assisted ventilation (2).

In the past, management of GBS was limited to supportive care, which included nursing and respiratory care, physical therapy, and maintenance of adequate nutrition. However, over the past two decades, treatment has evolved to include plasma exchange (plasmapheresis) and intravenous immunoglobulin (IVIG) (1). Both therapies have been shown to improve the rate of motor recovery (5). The patients most likely to benefit are those who present with moderate or severe progressive weakness, particularly children who are unable to walk, have a rapidly progressive course, or have bulbar paralysis and impending respiratory distress (1,2). Those with mild symptoms or with little progression typically have rapid and complete recovery, and do not require immunotherapy. Patients who present several weeks after the onset of illness are least likely to obtain benefit (1).

Plasma exchange is believed to work by removing antibodies against myelin and other soluble proteins from the circulation (1). The recommended protocol is 250 mL of plasma/kg divided into four to six sessions during the first week of illness, using albumin or fresh frozen plasma as replacement volume (2).

IVIG is generally preferred over plasmapheresis in children since IVIG does not require central venous access and does not decrease blood volume. IVIG has been safely administered in children as young as 2 years of age (1). The recommended dose is 2g/kg divided over two to four days (2).

Spontaneous recovery usually occurs 2-3 weeks after onset of disease, with most patients regaining full muscle strength and deep tendon reflexes. Residual weakness may remain in some patients. Improvement in strength usually occurs in reverse order, with bulbar muscle strength returning first and lower extremity strength returning last. Deep tendon reflexes are often the last function to recover (3).

The mortality rate is 2-5%, usually related to complications from ventilator-dependence or autonomic dysfunction (1). Factors associated with better outcomes include younger age at onset, milder clinical course, and slower progression of disease (9). With modern intensive care management and respiratory support, most children can be expected to have a full recovery from GBS.

Questions

1. What is the most commonly identified antecedent infection in Guillain Barre syndrome?
2. What is meant by albuminocytologic dissociation?
3. True/False: Improvement in strength occurs in the order in which it was affected.
4. Why is IVIG preferred over plasmapheresis in children?
5. When should a child with GBS be intubated?

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Answers to questions

1. Campylobacter jejuni enteritis.
2. Lack of cellular response (normal WBC count) in the CSF despite an elevated protein level. In the clinical setting of progressive flaccid paralysis, this is diagnostic of Guillain-Barre syndrome.
3. False. Improvement in strength occurs in reverse order (bulbar muscle strength returns first and lower extremity strength returns last).
4. IVIG does not require central venous access and does not decrease blood volume.

5. A child should be intubated if she/he has a rapidly decreasing vital capacity, dyspnea, fatigue, or deterioration of arterial blood gases. Dysphagia, shoulder weakness, and cardiovascular instability are also indications that mechanical ventilation may be necessary.

Chapter XVIII.8. Multiple Sclerosis
Lori S. Murayama

This is a 10 year old female who presents to the office with a chief complaint of clumsiness and blurred vision. She had been well until approximately 2 weeks ago when she noticed a loss of sensation and strength in her left leg, a rapid deterioration in vision, and a decrease in coordination. There is no history of fever, vomiting, or seizures. One year prior to this event, she presented to the hospital with poor coordination, dizziness and headaches. A left hemiplegia was noted as well as an asymmetric gait. A full recovery was made 5 days later, and she was discharged from the hospital without further treatment or a definite diagnosis.

Exam: VS are normal. Her weight, height, and head circumference are all at the 50th percentile. She is alert but subdued. Her HEENT exam is notable for severe visual loss and pale optic discs on funduscopy. Her heart, lungs, and abdomen are normal. She is noted to have a hyporeflexive paraparesis noted on the left.

She is hospitalized. A CT scan shows slightly enlarged ventricles, and an MRI scan shows multiple lesions in the periventricular white matter and cerebellum. Pattern visual evoked responses showed markedly delayed latencies. She is treated with corticosteroids and a full recovery results within a few weeks. Over the next 3 years, she has 2 more attacks with symptoms of right hemiplegia and bilateral visual loss. At the age of 15, she continues to be followed and has shown no further episodes.

Multiple sclerosis (MS) is an uncommon demyelinating disease characterized by focal disturbances in CNS function that usually follows a relapsing and remitting course. Because MS is known to most commonly affect adults in their 20's to 40's it is often an overlooked diagnosis in children. 3-5% of all MS cases are, however, diagnosed in patients below the age of 16 years, with 80% of these cases found between 10-15 years of age.

Although the exact cause of MS is unknown. It has been suggested that its etiology is multifactorial. One popular view is that MS is initiated by a viral infection in early life that alters a susceptible patient's immune status, thus predisposing him/her to develop an autoimmune CNS reaction to systemic infections. Although this is a widely held view, efforts to actually identify an infectious agent have been unsuccessful. In addition to speculation about a viral etiology, it has also been noted that MS occurs 10-20 times more in families of a MS patient than in the general population (1). There also appears to be a higher risk in females (2:1), people of western European descent, and those who lived in temperate (cold) climates before the age of 15. Thus it is believed that environmental (viral) as well as hereditary factors, a disordered autoimmune response, and the age of the individual at exposure plays a role in the pathogenesis.

The pathophysiology of the various neurological manifestations found in MS can be explained by multiple lesions disseminated throughout the CNS that spontaneously improve. Consequently, this also explains why the combination of signs and symptoms are limitless and why the symptoms often remit after a period of time.

Many of the clinical manifestations of childhood onset MS are similar to adult-onset MS (1). Table 1 below shows some of the symptoms found in the initial episode of MS in a study analyzing 56 children with MS. In general, visual disturbances such as blurring and diplopia are common in childhood MS with one study finding optic neuritis in 25-70% of children with MS (2). Paresthesia, motor disturbances, unstable gait, ataxia, vertigo, headaches, and sphincter problems also seem to predominate in childhood onset MS. Ghezzi et al. found that of 149 children who were diagnosed with MS before the age of 18, 25% had brainstem dysfunction, 18% had motor and sensory disturbances, and 9% had cerebellar disturbances (2). Transiently impaired consciousness and slowly progressive dementia have also been found in a significant number of children with MS (1).

Table 1: Number of children (out of 56) with these symptoms during the initial episode of MS (1):

Ataxia or muscle weakness:	31
Disturbance or vision (blurring, diplopia, blindness):	19
Numbness or paresthesia:	13
Dizziness, headache, vomiting:	10
Vertigo:	6
Urinary incontinence:	2
Facial weakness:	1
Hearing loss:	1
Partial seizures:	1

While there are many similarities found between childhood and adult onset MS, there are some clinical differences. Bye et al. found a higher incidence of partial seizures in childhood onset MS (3) and brainstem dysfunction had also been noted to be more frequent at the first attack in children. Vestibular symptoms, however, were noted to be less common in childhood MS (3).

There are numerous laboratory tests that can be used to help include/exclude MS, but no definitive diagnosis can be based just on these investigative findings. In terms of MRI and CSF abnormalities, childhood MS appears to be similar to adult onset MS. MRI findings are positive in 80% of cases with multiple lesions found in the brainstem, cerebellum, and central white matter (most notably in the periventricular region) on T2 weighted images. CSF examination reveals abnormalities in more than 2/3 of children with tests showing an elevated total protein, an increase in gammaglobulin, and electrophoresis revealing IgG oligoclonal bands in 85% of cases. Pleocytosis is also seen (50-100 lymphocytes per cubic mm) with a tendency to be more markedly elevated in childhood MS (1). Visual, brainstem auditory, and somatosensory evoked potentials support clinical suspicion as well, by demonstrating the existence of multiple demyelinating lesions within the CNS. These neurophysiological tests have been found to be abnormal in 70%, 50%, and 75% of MS children respectively (1).

Because of the endless combination of signs and symptoms in MS, its slowly progressive nature, and the lack of definitive investigative testing, diagnosing MS in children is often difficult. In order to establish a criteria for MS in adults, the Poser Committee created the following categories that can be applied to childhood onset MS as well:

1. Clinically definite MS: 2 attacks plus clinical signs or investigative evidence of 2 lesions.
2. Laboratory supported definite MS: 2 attacks plus clinical signs or investigative evidence of 1 lesion. Abnormal CSF (oligoclonal bands) is also found.
3. Clinically probable MS: 2 attacks plus clinical signs or investigative evidence of 1 lesion.
4. Laboratory supported probable MS: 2 attacks plus abnormal CSF (oligoclonal bands).

This diagnostic criteria are particularly useful in diagnosing MS in children because other demyelinating diseases can appear clinically similar. The following are some of the more common demyelinating disorders of childhood: Schilder's Disease, childhood MS, Devic disease (neuromyelitis optica), acute disseminated encephalomyelitis, acute necrotizing encephalomyelitis, central pontine myelinolysis, Leber optic atrophy, acute hemorrhagic leukoencephalitis, adrenoleukodystrophy.

Other diseases that should be considered in the differential diagnosis of MS include diseases with similar presentations. Disseminated lupus is one disease that can also produce recurrent hemiplegia. There are many other disease processes that fit in this category including Behcet's disease, arteriovenous malformation, vitamin B12 deficiency, and Lyme disease.

Until recently, there were not many treatment options available for children with MS and while there has been recent advancements in therapeutic interventions, most of the information has been derived from adult onset MS. The bottom line is that there is no cure for MS. There are, however, treatments available to shorten the duration of an attack, lengthen remission, and alleviate the symptoms.

Symptomatic treatment may be needed for treating spasticity, neurogenic bladder, bowel symptoms, pain, fatigue, and seizures. As for shortening the duration of acute relapses, corticosteroids can be used. It should be noted, however, that while corticosteroids speed the recovery from an acute attack, the actual extent of recovery is unchanged and it does not prevent future relapses.

In order to reduce the frequency of attacks for patients with relapsing-remitting or secondary progressive course of MS, beta-interferon or daily subcutaneous administration of copolymer I may be beneficial. Interferons such as Beta IB and IA lessens the frequency of relapses by 1/3 by down-regulating antigen recognition. However, like corticosteroids, it has no effect on the extent of disability. Copolymer I, a synthetic polypeptide, has also shown similar results with both showing the ability to decrease active and new lesions as demonstrated on MRI.

The natural history of MS can be unpredictable. Some children have only one attack during their childhood with many years of remission. Others have multiple recurrences that occur within a few months. In order to aid in the determination of prognosis, it is important to understand that the clinical course of MS can be divided into 4 categories:

1. Relapsing/remitting MS: A clearly defined disease that relapses with either full recovery or with sequelae and residual deficit on recovery.
2. Secondary progressive MS: A disease that initially follows a relapsing/remitting course but becomes progressive.
3. Primary progressive MS: A disease that progresses from the onset with only temporary plateaus and relatively minor improvements.
4. Progressive-relapsing MS: A disease that progresses from onset with clear acute relapses.

The prognosis of childhood MS appears to be similar to adult onset MS in terms of the clinical course, rate of progression and rate of relapses. In general, childhood MS presents primarily as a relapsing-remitting course, with one study finding that 56% of children had a relapsing-remitting course, 22% with a primary progressive course, and 22% with a mixed course (2).

In summary, MS is a common demyelinating disease that should not be overlooked in children. The etiology has not been fully elucidated, nor has a cure been found. Identification of the disease, determining its clinical course, and providing the appropriate therapies currently available, appear to be the essential clinical steps thus far.

Questions

1. True/False: Childhood MS most commonly occurs in children between the age of 10-15 years.

2. The etiology of MS is probably related to:
   a. A dysfunction in autoimmune regulation
   b. Environmental factors
   c. Hereditary factors
   d. All of the above

3. True/False: Visual disturbances is one of the most common manifestations of childhood MS.

4. True/False: Laboratory investigations usually provide a definitive diagnosis for MS.

5. True/False: Corticosteroids can speed the recovery from an acute attack.

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Answers to questions
1. True, 2. d, 3. True, 4. False, 5. True

Chapter XVIII.9. Hydrocephalus
Andrée M. Bouterie, MD

A 12 week old female infant presents to the emergency department with progressive vomiting, lethargy, and difficulty feeding over the past two days. Her mother reports that the infant has been increasingly irritable in the last week, and does not appear to be herself. She has been less interactive, and her cry has become more high-pitched and weak. She has not been breastfeeding well. Additionally, her mother is concerned because she thinks her infant's head has grown, and the "soft spot" on her head appears more tense. She thinks that the infant has felt "warm", but she has not measured the temperature with a thermometer. The infant has had fewer wet diapers and no bowel movements today.

She reports that the infant was born on time and that there were no prenatal or perinatal complications. The infant was released after a 48 hour stay in the regular newborn nursery, and had follow-up initially with her pediatrician about one week after discharge. She has had no further follow-up. From the previous medical records it is confirmed that the infant was born at term. There was poor prenatal care, but the labor and delivery were unremarkable. Mother's prenatal labs were normal. The infant weighed 2900 grams at birth (25th percentile), measured 47.8 cm in length (10th - 25th percentile), and had a head circumference of 34 cm (25th percentile).

Exam: VS: T 36.5 C, P 165, R 45, BP 98/65. Weight 4.20 kg (5th percentile), length 57 cm (10th - 25th percentile), HC 42.6 cm (95th percentile). In general this is a lethargic infant with a weak, high-pitched cry. Her head is oddly shaped and looks like an inverted pear. Her scalp veins are prominent, and the anterior fontanelle is tense and bulging. Eyes show pupils which are equal and round, but are sluggishly reactive to light. Red reflex is present bilaterally. EOMs are clearly dysconjugate. There is mild tachypnea with slight intercostal retractions. Lung fields are clear to auscultation bilaterally. Her heart exam reveals tachycardia with a regular rhythm and a grade 2/6 systolic ejection murmur at the left sternal border. Capillary refill is 2 seconds. Her spine is straight without protrusions or apparent defects. Her upper extremities show good tone and full range of motion with slightly brisk reflexes. Her lower extremities show increased tone with brisk reflexes bilaterally. There is 4+ clonus bilaterally. On neurologic examination, her eyes show rotated downward gaze bilaterally. There is a poor suck. The startle response is minimally present. The grasp and glabellar reflexes are present. No parachute reflex can be elicited. The Moro is present.

Imaging studies demonstrate hydrocephalus and aqueductal stenosis. A ventriculoperitoneal shunt procedure is performed by a neurosurgeon. Following surgery, the patient's anterior fontanelle is concave and the head circumference has decreased.

Hydrocephalus is the pathologic enlargement of the cerebral ventricles secondary to increased intracranial pressure caused by a mismatch between the production of cerebrospinal fluid (CSF) and its absorption (1). CSF is produced mostly by the ependymal cells of the choroid plexus within the ventricular system. CSF flows in a directional, pulsatile movement (2,3) from the lateral ventricles through the Foramina of Monro into the third ventricle. It then drains through the cerebral aqueduct (of Sylvius) into the fourth ventricle. CSF then exits the ventricular system through the Foramina of Luschka and Magendie, where it thereby gains access to the basilar cisterns, which communicate with the subarachnoid spaces over the cerebrum and spinal cord. Finally, CSF is returned to the vascular system by absorption through the subarachnoid villi and granulations.

A blockage of CSF along any point in this pathway may result in increased intracranial pressure and subsequent dilatation of the ventricular system upstream to the obstruction. Classically, hydrocephalus has been divided into two subtypes: communicating and non-communicating. Non-communicating hydrocephalus results from obstruction of CSF within the ventricular system. This includes obstruction at the outlet foramina of the fourth ventricles. Therefore, if CSF flow does not pass into the basilar cisterns, the corresponding hydrocephalus is classified as non-communicating. Some authors will utilize the term obstructive hydrocephalus to indicate non-communicating hydrocephalus.

Communicating hydrocephalus implies that there is free-flowing CSF within the ventricular system (and through its outlet foramina), and usually occurs secondary to impaired absorption at the subarachnoid villi and granulations. It should be noted from a pathophysiologic standpoint, however, that in almost every case, an obstructive process produces hydrocephalus. The single exception to this is the rare case of a congenital choroid plexus papilloma, where the mismatch between CSF production and absorption occurs as a function of excessive CSF production (1,3). Additionally, the term hydrocephaly should be distinguished from the terms macrocephaly and megalencephaly. Macrocephaly is a descriptive term for any head circumference larger than two standard deviations from the mean. Megalencephaly refers to an increase in brain parenchymal volume.

The differential diagnosis of hydrocephalus may be considered by age (3). Congenital hydrocephalus has an estimated incidence of about 3 to 4 per 1000 live births (4,5). The most common causes of congenital hydrocephalus are due to structural defects such as Chiari malformations and aqueductal stenosis (3,6). Dandy Walker is also an important cause of congenital hydrocephalus, although it occurs less frequently. Additionally, intrauterine infections, especially toxoplasmosis, rubella, cytomegalovirus, and syphilis, may be associated with congenital hydrocephalus. In the neonatal period, acquired causes of hydrocephalus include perinatal infections and intracranial bleeding secondary to trauma or anoxia. Premature infants are particularly susceptible to intraventricular hemorrhage (IVH), which may subsequently lead to hydrocephalus. AV malformations of the Great Vein of Galen, or the straight sinus may also present in this period and may cause hydrocephalus secondary to blockage or rupture. Much less common causes of hydrocephalus in the neonatal period

include arachnoid cysts, congenital choroid plexus papillomas, and tumors (1,3). The common causes of congenital and neonatal hydrocephalus will be discussed below.

Chiari malformations are a very common cause of congenital hydrocephalus, and account for up to 40% of cases (3). Chiari malformations refer to a set of congenital anomalies of the hindbrain where there is a downward displacement of the brainstem and cerebellum through the foramen magnum. There are three types depending on the degree of herniation though the foramen (1,7). Chiari type I is caudal displacement of the cerebellar vermis or tonsils through the foramen. In type II, the fourth ventricle and lower medulla are also herniated. The Chiari type III malformation involves extension of the cerebellum through the foramen magnum and into an associated cervical spina bifida. Chiari type II is the most common of the Chiari lesions and almost always occurs in conjunction with a myelomeningocele and hydrocephalus (1,7).

Aqueductal stenosis is also a very common cause of congenital hydrocephalus. With an occurrence of 0.5 to 1.0 per 1000 live births, it accounts for approximately 20% of hydrocephalus cases (3). Although commonly recognized at birth, the disorder may have an insidious onset, and should be considered in the differential diagnosis of hydrocephalus at any age. Aqueductal stenosis refers to narrowing of the fourth ventricular aqueduct of Sylvius and results in obstructive, non-communicating hydrocephalus. One form of aqueductal stenosis, associated with a syndrome called X-linked hydrocephalus, is caused by a mutation of the X-linked recessive L1 gene, which is responsible for the production of specific neuronal cell adhesion molecules (3,6). Aqueductal stenosis may also be associated with gliosis, which results after destruction of ependymal cells after a hemorrhagic or viral infectious process. Hydrocephalus that occurs as a result of toxoplasmosis or cytomegalovirus is usually the result of aqueductal stenosis (4). There are also multiple case reports of aqueductal stenosis after viral encephalitis caused by mumps (9,10,11).

The Dandy-Walker malformation is a cystic dilatation of the fourth ventricle following partial or complete agenesis of the cerebellar vermis, which leads to obstruction of CSF outflow though the foramina of the fourth ventricle. The syndrome occurs in approximately 1 per 30,000 live births (2,3), and is associated with less than 5 percent of all cases of hydrocephalus (4). Although the defect is present at birth, hydrocephalus does not always present in the neonatal period. Approximately 80% of all Dandy-Walker malformations will be diagnosed by one year of age, although some diagnoses may be delayed until adolescence or adulthood (3,12).

Intraventricular hemorrhage (IVH) is becoming an increasingly important cause of hydrocephalus secondary to the increased survival of very low birth weight infants (<1,500 grams) (13). Intraventricular hemorrhage is the result of vascular instability of cerebral vessels in the germinal matrix at the level of the head of the caudate in the premature infant. Bleeding of these vessels has been classified into 4 grades. Grade I is hemorrhage within the germinal matrix only. Grade II is hemorrhage from the matrix into the ventricles, but without ventricular dilatation. Grade III is IVH with resultant ventricular dilatation. Grade IV is IVH with ventricular dilatation and extension of the bleeding into the surrounding brain parenchyma. When present, IVH usually occurs in low birth weight infants within 72 hours of delivery, and 50% of these occur without immediate clinical symptomology (13). Post-hemorrhagic hydrocephalus may occur immediately as a result of clotting of blood in the ventricular system, which leads to obstruction. More commonly, however, communicating hydrocephalus develops within weeks to months after the hemorrhagic event as the breakdown products of blood lead to diffuse fibrosis of the leptomeninges (13). In order to detect asymptomatic intraventricular hemorrhage, it is recommended that all premature neonates of gestational age <30 weeks of life undergo screening cranial ultrasound at 7 to 14 days of life. If none is detected, a follow-up cranial ultrasound is recommended at 36 to 40 weeks postconception (14).

After the newborn period, common causes of hydrocephalus are hemorrhage, and post-viral or post-bacterial meningitis. The mechanism of formation of hydrocephalus secondary to hemorrhage in other age groups is the same as for premature infants described above, except that the origin of bleeding is different and may be due to rupture of an AV malformation, subarachnoid bleed, or as a result of a traumatic injury. In bacterial meningitis, clumping of increased cellular and infectious matter within the CSF may produce non-communicating hydrocephalus. However, communicating hydrocephalus that occurs as a result of permanent scarring of the meninges is the most common outcome, and occurs in up to 1% of survivors of bacterial meningitis (5). Tumors, cysts, and other space occupying lesions should be considered in the differential diagnosis of hydrocephalus at any age, although they become more important causes in this age group.

The signs and symptoms of hydrocephalus may also be considered as a function of age. The most visually dramatic cases of hydrocephalus occur in infants prior to the close of the anterior fontanelles at 18 months, where the increase in head size may become very large secondary to decreased containment of swelling by open sutures. Subsequently, limited expansion of the more developed sutures leads to earlier neurologic signs, which promote detection of lesions prior to the onset of massive hydrocephalus. Before 2 years of age, hydrocephalus will invariably present with some enlargement of the head. There may be cephalofacial disproportion, possibly with frontal bossing. Sutures may be splayed, and scalp veins may be very prominent. The "setting sun" sign is an ocular abnormality where the eyes appear to look downward such that the whites of the sclera form an arc above the irises. Papilledema is a rare finding; however, long-standing hydrocephalus may be associated with optic atrophy. In infants, primitive reflexes may persist and there may be delayed development of the more mature reflexes. Motor spasticity with hyperreflexia and clonus may be present and will be more prominent in the lower extremities before the upper extremities. This is secondary to increased stretching of the motor fibers of the lower extremities as they traverse longer pathways (1,3). It should be noted that if the onset of hydrocephalus is acute with rapid progression, then vomiting, lethargy, seizures, and cardiorespiratory compromise may occur in infants despite open sutures (3). In older infants, pressure on the brainstem bilaterally may lead to a condition known as pseudobulbar palsy where poor oral-motor control is manifest by difficulty with swallowing and changes in speech.

In older children with hydrocephalus, more focal neurologic signs will be apparent and suggestive of the lesion. Older children present with more classic signs of increased intracranial pressure such as headache and vomiting that is worse in the morning especially upon wakening. Papilledema and strabismus will likely be present. The "bobble head doll syndrome" is a manifestation of obstructive lesions around the third ventricle or aqueduct and is characterized by 2 to 4 oscillations of the head per second along with psychomotor retardation (2,3). Spasticity is particularly prominent in the lower extremities, and there may be a positive Babinski sign. Endocrine abnormalities may be apparent due to long-standing perturbation of the hypothalamic-pituitary axis and may result in growth derangements, delay or acceleration of sexual maturity, fluid and electrolyte disturbances, and thyroid dysfunction (2,3). Cognitive deficits may be suggestive of the lesion, and emotional lability may be a presenting sign.

The diagnosis of hydrocephalus is made more readily apparent with the increasing availability of imaging techniques. Ultrasonography may be used to detect hydrocephalus in the fetal and neonatal periods. In older infants and children, computed tomography (CT) may be utilized. However, magnetic resonance imaging (MRI) is the preferred diagnostic tool in this age group as it provides superior resolution of the brain, spinal cord, and subarachnoid spaces such that specific lesions are more easily detected (3,15). The characteristic lesion of non-communicating hydrocephalus will show dilatation of the ventricles proximal to the site of obstruction

with periventricular edema of the adjacent white matter caused by disruption of the ependymal lining in the affected area. In communicating hydrocephalus, the entire ventricular system will be dilated with distinct enlargement of the subarachnoid space over the cerebrum.

Once the underlying etiologic condition has been addressed, the mainstay of therapy for progressive hydrocephalus is a shunt procedure, which allows for diversion of CSF with the overall goal of ventricular decompression. In general, CSF fluid proximal to the site of obstruction is shunted through a catheter and drained into a body space that allows for absorption of the ventricular fluid. The most common and preferred site of drainage is into the peritoneum (VP-ventriculoperitoneal shunt), although many other sites have been utilized (16,17). The most common secondary sites are the pleural space and the venous system or right atrium. The shunt catheter contains a valve to assure one-way CSF flow and is concealed within a subcutaneous tract. Extra tubing is usually curled into position at the distal catheter end to allow for growth of the infant or child. Other treatments for hydrocephalus include the endoscopic third ventriculostomy, which involves fenestration of the third ventricle in obstructive hydrocephalus to provide a direct communication with the subarachnoid space. Additionally, lumboperitoneal shunts may be utilized in cases of communicating hydrocephalus (16,17).

Medications that reduce intracranial pressure such as mannitol may be utilized for cases of rapidly progressive hydrocephalus as a palliative measure while awaiting surgery. Additionally, specific medications that decrease the production of CSF may be useful such as acetazolamide and furosemide. These latter medications may also be utilized temporarily for slowly progressive hydrocephalus or hydrocephalus that is transient, e.g., while awaiting shunt revision (1,16).

Shunt malfunction is a fairly common occurrence with a one-year failure rate of 30-40% (18,19). Higher rates of failure have been described in younger patient populations with the most significant risk occurring in patients younger than 6 months of age at the time of implantation (18,20). The most common time for shunt failure to occur is within six months of surgery (18,21), and causes of shunt malfunction include obstruction, infection, and over-drainage (16,18,21). Obstruction occurs generally because of collection of organic matter in the catheter tubing. Symptoms of shunt malfunction include headache and vomiting. Sunsetting of the eyes, vision changes, diplopia, and distended veins may also be noted. CT scanning is fairly reliable in identifying shunt malfunction. Enlargement of the ventricles is diagnostic of shunt malfunction. Unfortunately, a baseline CT (i.e., when the shunt is working) is not always available for comparison. Frequently, the patient's previous CT scans were obtained when the shunt was malfunctioning. This must be taken into consideration when comparing the size of the ventricles.

Infections usually come to attention about two months after shunt insertion, suggesting that infection may be occurring at the time of surgery, although subsequent infection through contaminated skin surfaces also occurs (2,18). Infection rates vary from 1-10% (3,18,20,21). The most common causative agent of infection is coagulase-negative staphylococci, especially Staphylococcus epidermidis, although Staphylococcus aureus has also been implicated. Treatment usually mandates removal of the shunt, and intraventricular as well as intravenous antibiotics may be required. If shunt revision is necessary, sterility of the CSF is first documented by culture prior to surgery. In cases of community-acquired meningitis, however, treatment may be given as usual with the shunt left in place, as the usual causative agents are unable to colonize the shunt and the catheter may actually lessen the severity of symptoms (16,20).

The overall outcome and prognosis of hydrocephalus is highly dependent on multiple factors including the age of onset, etiology, ventricular expansion, and extent of neurologic damage prior to correction of the intracranial insult. Mortality rates have been reduced to less than 5% in ten years after shunt placement (22). In one study of 129 children followed ten years post-operatively, who had had shunts placed prior to the age of two, 60% were found to have motor deficits, 25% had visual or auditory deficits, and 30% had epilepsy (22). About 1/3 of children had IQs above 90, 28% had IQs between 70 and 90, and another 30% had IQs below 70. Twenty-one percent had IQs less than 50. The presence of behavioral disorders was frequent in this study. Other researchers have also found a relationship between hydrocephalus and behavior problems (23,24). Among higher functioning children, a discrepancy has been noted between verbal and nonverbal (performance) IQs, with nonverbal skills being reduced in hydrocephalic children (23,24,25,26). It has been postulated that disruption of cerebral white matter tracts leads to this decrease in nonverbal skills, which may promote behavioral maladjustment in these children. These studies indicate that despite the decreased mortality associated with hydrocephalus, there is still much long-term morbidity associated with the disorder. Multidisciplinary planning and close follow-up is needed to ensure the maximal developmental potential of these children.

Questions

1. Define hydrocephalus and distinguish this term from macrocephaly and megalencephaly.
2. What are the two classic classifications of hydrocephalus and give examples of each?
3. What are the most common causes of congenital hydrocephalus?
4. What is X-linked hydrocephalus?
5. True/False: The Dandy-Walker syndrome is usually diagnosed at birth.
6. What is the purpose of routine cranial ultrasound screening in the very low birth weight infant?
7. True/False: CT is the best imaging method for the diagnosis of hydrocephalus after the neonatal period?
8. What is the frequency of shunt failure after initial surgical treatment of hydrocephalus?
9. What is the rate of infection after shunt insertion, and what is the most likely etiologic agent?
10. True/False: Most children with hydrocephalus go on to have IQs consistent with mental retardation.

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Answers to questions

1. Hydrocephalus refers to pathological enlargement of the cerebral ventricles secondary to a mismatch between the amount of production of CSF and its drainage. Macrocephaly is a general term for any head circumference greater than two standard deviations from the mean. Megalencephaly refers to increased volume of the brain parenchyma.

2. Hydrocephalus is divided into two types: communicating and non-communicating. Communicating hydrocephalus is used if CSF flows freely throughout the ventricular system. Non-communicating hydrocephalus indicates that obstruction of CSF occurs somewhere within the ventricular system, including the outlet foramina of Luschka and Magendie. Communicating hydrocephalus may occur from scarring of the leptomeninges after viral or bacterial meningitis, or after a hemorrhagic brain event where the breakdown products of blood lead to diffuse fibrosis of the meninges. Non-communicating hydrocephalus occurs in cases of discreet obstruction within the ventricular system, such as occurs with aqueductal stenosis, the Chiari Malformations, the Dandy-Walker malformation, or mass effect from brain tumors or other mass lesions.

3. The most common causes of congenital hydrocephalus are Chiari malformations and aqueductal stenosis.

4. X-linked hydrocephalus is a form of aqueductal stenosis in which there is a mutation on the X-linked recessive L1 gene, which produces a family of abnormal neuronal cell adhesion molecules that leads to narrowing and obstruction at the level of the cerebral aqueduct.

5. False. The Dandy-Walker malformation, although present at birth, is responsible for less than 5% of cases of congenital hydrocephalus. Approximately 80% of cases will eventually be detected by one year of age.

6. When present, intraventricular bleeding in the very low birth weight infant usually occurs within the first 72 hours of life. Because up to 50% of these events will occur without immediate clinical symptomology, it is recommended that routine screening be performed between days 4 to 7 of life.

7. False. MRI is the preferred imaging method for the diagnosis of hydrocephalus after the neonatal period as it will also elucidate more precisely than CT the specific etiology of the hydrocephalus. However, in an emergency situation, CT is preferred because it can be done rapidly.

8. Shunt malfunction is a fairly common occurrence with a one-year failure rate of 30 to 40%.

9. The rate of infection after shunt insertion varies among different institutions, and has been reported from 1 to 10%. The most likely etiologic agent is Staphylococcus epidermidis.

10. False. The overall outcome and prognosis of hydrocephalus is highly dependent on multiple factors, including age of onset, etiology, the rate of ventricular expansion, and the extent of neurologic damage prior to shunt placement or other corrective intervention. In one study that looked at 129 children 10 years after shunt placement (shunts were placed prior to age two), approximately 60% had IQs over 70, which is generally considered the cutoff for one of the diagnostic criteria for mental retardation.

Chapter XVIII.10. Neural Tube Defects
Mari Uehara, MD

A C-section is scheduled for a 16 year old G1P0 mother at 37 weeks. Prenatal care was not sought until 32 weeks gestation. Mother did not take any vitamins or folate supplements prior to that time. Initial prenatal lab studies were significant for an elevated alpha fetoprotein. A prenatal ultrasound done at 34 weeks demonstrated a meningomyelocele. No hydrocephalus was noted at that time. A neurosurgeon was consulted. A C-section is scheduled to deliver the infant as non-traumatically as possible with the availability of the neurosurgeon close by.

At delivery, the infant is delivered with Apgar scores of 7 and 8. Birthweight is 3.2 kg. A translucent membrane sac overlying the mid-lumbar region is noted. It is leaking xanthochromic fluid. Upper extremity movement is noted to be good, but lower extremity movement is not as vigorous. The infant is transferred to the NICU where vascular access is obtained and initial stabilization measures are performed. Five hours later, the infant is taken to the operating room where a neurosurgeon closes the meningomyelocele defect over the lower back. Post-operative recovery in the NICU is unremarkable. Lower extremity movement is moderate. A head ultrasound study shows mild hydrocephalus. Two months later, the hydrocephalus is worsening on ultrasound, so a VP shunt is surgically placed.

Neural tube defects (NTDs) are a group of birth defects which are associated with a defective closure of the neural tube and the subsequent development of the central nervous system (brain and spinal cord). It is one of the most common birth defects occurring in approximately 0.7-1.0 per 1000 live birth each year (1,2). There are three types of NTDs: anencephaly, encephalocele, and spina bifida. Spina bifida, the most common NTD, means "split spine" in Latin and is a result of failure of the neural tube to close during the 3rd-5th week of pregnancy. The terminology can be confusing since multiple terms have been used for various conditions depending on the extent of the involvement of the spinal cord and surrounding structures.

Spinal dysraphism and spina bifida apply to a heterogeneous group which has defects of closure affecting the spinal canal (which may encompass the meninges and spinal cord itself in addition to bony vertebral elements). Myelodysplasia refers to defects of spinal cord development, which commonly occurs with spina bifida; however not necessarily associated with failure of fusion of the arches of the vertebral spine, so this could include entities such as syringomyelia and diastematomyelia. Spina bifida occulta is the simple failure of fusion of the spinal arches (i.e., bony involvement only), such that the neural elements are covered by skin and do not protrude above the level of the back. Occult spinal dysraphism means that spina bifida occulta is present with overlying cutaneous markers such as dimple, fistula, hair patch, and hemangioma. These markers may indicate the presence of cord tethering with a lipoma or a dermoid cyst. Spina bifida cystica is the commonest type of NTD which includes meningocele, meningomyelocele/myelomeningocele, lipomyelomeningocele. A meningocele is a lesion which does not involve neural elements in the cystic outpouching of the meninges. Meningomyelocele or myelomeningocele means that dysplastic neural elements protrude through the unfused vertebral arches. It can be completely covered with meninges and skin (closed meningomyelocele) or there may be a connection of spinal fluid to outside (open meningomyelocele). Lipomeningocele and lipomyelomeningocele are closed meningomyelocele with overgrowth of fatty tissue involving the meninges alone or including the spinal cord. The term spina bifida is ambiguous in that it is often used to describe conditions from spina bifida occulta to spina bifida with myelomeningocele.

The manifestations of the spina bifida depend on the level of the spinal cord involvement at which neural tube closure was incomplete. The lesion is located in lumbosacral area in more than 80% of the cases (3).

Children with the less common thoracic lesions, have flaccid paralysis of lower extremities with variable weakness in abdominal and trunk musculature. These defects are frequently associated with serious complications (e.g., respiratory compromise). Children with high lumbar lesions (L1, L2) have flaccid paralysis of knees and ankles and may walk with extensive braces and crutches. Children with midlumbar lesions (L3) have paralyzed ankles and toes. These children can accomplish independent ambulation with braces. Children with low lumbar lesions (L4, L5) often have weak ankle and toe mobility. They are particularly prone to ankle or foot deformities and often need orthosis for independent ambulation.

Bladder and bowel problems are present in more than 90% of children with meningomyelocele regardless of the level of lesion (1). Some children may have problems with bladder emptying, while others may have problems with storing the urine adequately. Despite the type of neurogenic bladder, it is crucial to prevent urinary tract infections and protect the upper urinary tract since renal failure is one of the important causes of death among these children. Bowel continence requires normal external sphincter control, internal sphincter reflex relaxation, rectal sensation and colonic motility. Lack of sensation and inability to control external sphincters makes these children unable to sense or control stool passage. Bowel management programs with regularly scheduled toileting, use of stool softeners, and dietary measures (i.e., additional fiber) are important to avoid constipation and soiling.

Spina bifida is often not only an isolated birth defect of the spinal cord and spine, but there commonly are associated congenital malformations of the brain. Hydrocephalus is a major complication of meningomyelocele and is present at birth in 85-95% of cases as shown by ultrasonography (3,4). These children with hydrocephalus require ventriculoperitoneal shunt (VP shunt) placement. Shunt malfunction and infection are frequent complications and most children eventually require shunt revision (30-40% within one year of insertion of the shunt). Lethargy, vomiting, irritability, bulging and tense fontanelle, and headache, are common symptoms of shunt malfunction. Seizures also occur in up to 17% of the children with meningomyelocele and almost always occur in those with hydrocephalus (5).

Arnold-Chiari II malformation (the cause of the hydrocephalus) is present in the majority of children with meningomyelocele. The cerebellum and medulla oblongata are shifted caudally, so this resultant packing into the cervical spinal canal results in deformation. The symptoms are due to progressive hydrocephalus (if untreated) and dysfunction of the lower cranial nerves, respiration and swallowing. Hydrocephalus occurs in most children secondary to aqueductal stenosis or obstruction to CSF flow around the medulla.

Any clinical changes in children with meningomyelocele should prompt a search for an underlying cause. By far, the most common cause of deterioration is shunt malfunction. Another important cause is tethering of the spinal cord. Up to one third of children with myelodysplasia may experience spinal cord tethering. A tethered spinal cord results from traction on the conus medullaris and cauda equina, which causes spinal cord stretching and ischemia with subsequent loss of neurological function. Symptoms of a tethered spinal cord include spasticity, weakness, decreased sensation in the lower extremities, changes in urinary and bowel functions, or back pain, progressive scoliosis and foot deformity. Some children with occult spinal dysraphism (i.e., no overlying meningomyelocele) are asymptomatic and truly have an occult spinal cord condition. An MRI scan will identify the spinal abnormality. Surgery is indicated in

symptomatic patients. Prophylactic intervention among asymptomatic children can prevent the long-term disabilities associated with this condition.

Mastery of bowel and bladder continence is crucial to optimal functioning and is of the major importance for social acceptance. The voiding program may include medications, intermittent catheterization, and possibly operative reconstruction. Clean intermittent catheterization is the most commonly used method to help urinary continence. It is used to remove residual urine, improve urinary drainage, and provide decompression. The goal is to have this task accomplished by early school age. A child's physical abilities and psychological readiness for toileting should be assessed and continued assistance may be necessary for some children.

Children with physical disabilities are often described by their disabilities, and not by their strengths or abilities, which are also important. Children with spina bifida are often automatically placed in regular classes or classes for children with orthopedic problems. Although this is frequently the best placement, there are children whose orthopedic problems are secondary and their learning disability associated with spina bifida may be the major disability. Children with spina bifida and hydrocephalus may have problems with motor skills, attention, memory and organization. These issues should be understood and addressed in the Individualized Education Program (IEP).

Latex allergy has been common among children with spina bifida (about 20-70%) (6). Although the cause of latex allergy in children with spina bifida is not known, it may be due to the early, intense, constant exposure to rubber products among these children. Latex comes from the sap of the rubber tree Hevea brasiliensis. After the commercial purification process there are small amount of residual proteins that could cause allergy symptoms ranging from mild skin rashes or sneezing to hives, respiratory distress and anaphylactic shock. Many products contain rubber components of which we are unaware and environmental exposure to rubber products in both the community and hospital is widespread (e.g., rubber bands, erasers, gym mats, certain paints and glues, elastic waist or leg bands in clothing and disposable diapers). There are some food items (e.g., bananas, avocado, chestnuts) which can also cause cross-reactions. Prevention is the best approach. This allergic condition should be documented on medical and school records, communication devices such as medical alert bracelet should be provided as well as auto-injectable epinephrine as a part of the emergency plan for these children. In fact, it is commonly recommended that all children with spina bifida and/or myelodysplasia be kept latex free even if allergy has not yet been demonstrated.

The initial treatment for spina bifida is early surgical closure of the defect. Because of the multisystem involvement of this condition as stated above, management of this condition requires a comprehensive, multidisciplinary team approach. This team may include pediatricians, nurses, specialists (neurologists, neurosurgeons, urologists, orthopedists, developmental-behavioral pediatricians), physical therapists, occupational therapists, social workers, and special education teachers.

Alpha-fetoprotein (AFP) is elevated in maternal serum (MSAFP) and amniotic fluid (AFAFP) in open NTDs such as encephalocele, meningomyelocele and anencephaly. It is also increased in other conditions such as abdominal wall defects (gastroschisis and omphalocele). AFP becomes measurable in maternal serum at the end of first trimester. Maternal blood sample measurements are collected between 16-18 weeks of gestation to provide enough time for more definitive testing as necessary and to allow sufficient time for decision making regarding continuation or termination of an affected pregnancy. The MSAFP level is affected by gestational age and the number of fetuses. Elevated AFP level in amniotic fluid is more definitive than MSAFP, identifying 90-95% of affected fetuses with open NTDs. Acetylcholinesterase assay is more specific for neural tissue with a 99% accuracy rate. Ultrasonography also has been increasingly accurate in prenatal diagnosis of fetal anomalies.

Folic acid is a synthetic compound used in dietary supplements and fortified foods. The term folate includes all compounds that have the vitamin properties of folic acid (folic acid and naturally occurring compounds in food). The average diet in the United States contains 200 microgram of naturally occurring folate, which is less bioavailable than folic acid. Studies have demonstrated that 50% or more NTDs can be prevented if women consume a folic acid supplement before and during the early weeks of pregnancy. The American Academy of Pediatrics endorses the US Public Health Service recommendation that all women capable of becoming of pregnant consume 400 microgram of folic acid to prevent NTDs.

Studies have shown improved long term outcome regarding ambulation, urinary continence, and social continence of stool. One of the studies also showed that about 60% of children with spina bifida attended regular school programs. These outcomes depend on the level of lesion and the severity of complications.

Questions

1. True/False: Vitamin supplementation prior to pregnancy has been found to reduce the risk of neural tube defects.
2. True/False: Spina bifida patients have neurogenic bladders.
3. True/False: Hydrocephalus develops in meningomyelocele patients because of cord tethering.
4. True/False: Children with meningomyelocele have a high risk of developing latex allergy, therefore, they should not be exposed to latex from birth.
5. True/False: High meningomyeloceles result in lower extremity paralysis, but most patients with low lying meningomyeloceles are able to ambulate on their own or with assistive devices.

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9. Spina Bifida Association of America, 4590 MacArthur Blvd., NW, Suite 250, Washington, DC 20007-4226, phone (800)621-3141, e-mail: sbaa@sbaa.org

Answers to questions

1. True. Folate supplementation prior to pregnancy and in early pregnancy reduces the risk of neural tube defects.
2. True, in that nearly all patients with myelodysplasia have bladder/bowel dysfunction; however, patients with spinal bifida occulta may only have a vertebral anomaly, without myelodysplasia, in which case, their bladder function will be normal.
3. Controversial question, but probably false. The hydrocephalus is usually due to a Arnold Chiari malformation in the brain (the other end of the neural tube) which results in hydrocephalus. It is probably not cord tethering which causes the hydrocephalus.
4. True.
5. True.

Chapter XVIII.11. Neurofibromatosis
Vince K. Yamashiroya, MD

A 6 month old infant female is seen in your office as a new patient for a well baby visit. Her family moved from here from Asia recently, where she was born. There were no prenatal or postnatal complications, and she has had no significant medical problems since birth. Her family history is positive for her father who has a condition in which his body is covered with fleshy small growths, similar to skin tags, and on the father's side, there are several family members with the same warty growths, seizures, and high blood pressure.

Exam: VS are normal. Her growth parameters are in the 25-50th percentiles. Her examination is otherwise unremarkable except for multiple coffee colored spots on her trunk and abdomen.

You suspect neurofibromatosis based on her cutaneous findings and the family history. You schedule her for a follow up visit tomorrow to discuss this further. You have overnight to prepare yourself to initiate a proper evaluation and treatment plan, and to counsel the family.

Neurofibromatosis is one of the more common types of neurocutaneous syndromes that is well known because of its clinical features. Its hallmark sign is the neurofibroma, which is a tumor of nerve connective tissue (1). There are actually two types of neurofibromatosis. The first type is NF-1, which is the most common type and its clinical features include cafe au lait spots and neurofibromas. The second type, NF-2, only accounts for 10% of the cases of neurofibromatosis, and its clinical feature is bilateral vestibular schwannomas (or acoustic neuromas), with cafe au lait spots and skin neurofibromas being less common (2). Neurofibromatosis was recognized as a disease for well over a hundred years. In 1882, Friedrich von Recklinghausen published his famous monograph describing this entity, and this disease became known as von Recklinghausen disease, which is NF-1. Other people have also recognized this disease as early as the eighteenth century, such as Tilesius and Akenside. In 1981, Dr. Vincent Riccardi recognized NF-2 as a clinically distinct entity from NF-1 (3).

Today, we know much more about both types of neurofibromatosis. Through molecular genetic studies, it was discovered in 1990 that the NF-1 gene is on the long arm of chromosome 17 and encodes for a protein called neurofibromin. It is believed that perhaps the NF-1 gene is a tumor suppressor gene, and that neurofibromin allows for the dephosphorylation of ras-GTP to ras-GDP. In patients with NF-1, there is a mutation in the NF-1 gene, therefore ras, which is thought to be a proto-oncogene, is not dephosphorylated and sends intracellular signals to inhibit apoptosis (programmed cell death) and stimulate cellular proliferation (4). The NF-2 gene was discovered in 1987 to be in the long arm of chromosome 22, and in the 1990's, its gene product was determined to be in the band 4.1 families of proteins that are associated with the cytoskeleton; however the function of the NF-2 gene is still not known (5).

We do know that both types of neurofibromatosis are autosomal dominant, just like tuberous sclerosis, which is another type of neurocutaneous syndrome. Interestingly, new mutations occur in about 50% of patients with NF-1 (6) and NF-2 (7), making these gene loci one of the highest known mutation sites in humans.

NF-1 is one of the most common types of neurocutaneous syndromes, with an incidence of 1/4000 (2). There is no sex or ethnic predilection (8). NF-2, on the other hand, is uncommon, having an incidence of about 1 in 40,000 births (7). This type of neurofibromatosis usually presents later in life, and is therefore seen by internists, rather than pediatricians.

The diagnosis of NF-1 is still a clinical one, despite the recognition of the gene causing NF-1 and its gene product. In 1987, the U.S National Institutes of Health Consensus Development Conference developed a list of criteria for the diagnosis of this disease. NF-1 is present in a patient who has two or more of the following signs:

1. Six or more cafe au lait macules greater than 5 mm in greatest diameter in prepubertal individuals or >15 mm in greatest diameter after puberty.
2. Two or more neurofibromas of any type or one or more plexiform neurofibromas (see definition below).
3. Freckling in the axillae or inguinal region (Crowe sign).
4. A tumor in the optic pathway.
5. Two or more Lisch nodules (iris hamartomas).
6. A distinctive osseous lesion, such as sphenoid wing dysplasia or thinning of the cortex of the long bones (with or without pseudoarthrosis).
7. A first degree relative (parent, sibling, or offspring) with NF-1 by the above criteria.

The signs of NF are age-dependent, with more signs appearing at older ages. Because of this, about 90% of children who are older than six years of age can be diagnosed using these criteria, but younger children may be missed (9).

Neurofibromas are benign tumors arising from large and small nerves, and are a cardinal feature of neurofibromatosis. They are mainly composed of Schwann cells and fibroblasts, and can occur anywhere in the body outside of the brain and spinal cord proper. There are four different types of neurofibromas: discrete cutaneous neurofibromas, discrete subcutaneous neurofibromas, deep nodular

neurofibromas, and diffuse plexiform neurofibromas. The cutaneous neurofibromas are sessile or pedunculated masses on the skin, which are fleshy and non-tender, and can vary in size. The subcutaneous neurofibromas lie deeper and look like bumps on the skin, which can sometimes be tender. The deep nodular neurofibromas involve tissues and organs underneath the dermis, and resemble cutaneous and subcutaneous neurofibromas. The diffuse plexiform neurofibromas differ from the others in that it has fronds that penetrate normal tissue, making them difficult to remove. These plexiform neurofibromas can vary in severity from no skin involvement to severe disfigurement, sometimes resulting in elephantiasis with limb hypertrophy or severe facial disfigurement. The deep nodular neurofibromas and diffuse plexiform neurofibromas share a common feature in that they can become malignant peripheral nerve sheath tumors. The single most important sign that a tumor has become malignant is persistent, unexplained pain. Neurofibromas can occur at any time of life, although the cutaneous, subcutaneous, and deep nodular types usually appear in late childhood to early adolescence, and sometimes later. The number and size of the neurofibromas increase throughout middle and late adulthood. By 16 years of age, all patients will have cutaneous and/or subcutaneous neurofibromas. The ones that occur earlier in life are the diffuse plexiform neurofibromas, which are actually thought to be congenital. An interesting finding is an abnormal hair whorl over the spine, called the Riccardi sign, which represents a congenital paraspinal plexiform neurofibroma, which can lead to dysplastic scoliosis later in life (8,10).

Cafe au lait spots are spots with the color of coffee with milk, being tan colored. They can vary in size from smaller than 10 mm to as big as covering a body part on one side, although the typical lesions are 1-3 cm ovoid spots, which are uniform in color. They can occur anywhere on the body except for the scalp, eyebrows, palms, and soles. Histologically, they are giant melanosomes within melanocytes. Although they are a hallmark feature of NF-1 and occur in almost all individuals with this disease, they can also be seen in normal individuals as well. They are usually one of the first signs that will alert the clinician to the presence of NF-1 since they usually appear at the time of birth (11).

Axillary freckling is akin to cafe au lait spots except they are smaller, about 1 to 3 mm in size, and occur in clusters. They usually appear in intertriginous areas like the axillae, inguinal area, upper eyelids, the base of the neck, breast folds in women, and skin folds in obese patients.

Lisch nodules are another characteristic finding of NF-1 occurring more frequently as an affected individual ages. In those who are 5 years old, the frequency is 25%, at age 10 years it is 50%, and by age 20 years it is more than 95%. They are pigmented hamartomas appearing as translucent masses with a gray-tan hue due to the melanin-containing cells that are on the iris. Usually they are bilateral and do not affect vision. Lisch nodules are diagnostic for NF-1, and they can be seen on slit-lamp examination by an ophthalmologist.

Optic gliomas are benign tumors which can form anywhere along the optic tract from the globe all the way to the optic radiations out of the occipital lobe. They occur in about 15% of NF-1 patients, but only 33% of these are symptomatic. These symptoms include decreased visual acuity, visual field deficits, proptosis, strabismus, optic atrophy, headache, nausea, anorexia, hypothalamic dysfunction, and precocious puberty. Current recommendations are for patients to have a full ophthalmologic examination when first diagnosed with NF; follow-up full ophthalmologic examination annually up to age 6 years; tests for visual acuity, color vision (Ishihara test), and slit-lamp examinations at 8, 13, and 20 years of age; and full ophthalmologic examinations at 10, 16, and 25 years of age. If a tumor is suspected, then neuroimaging is indicated. If an optic glioma is asymptomatic, then it can be observed. However, if it becomes progressive or symptomatic, then surgery, medical, or radiation therapy should be considered.

Neurofibromatosis should be considered a multiorgan disease in that tumors can occur in any part of the body. Other manifestations are hypertension from renal artery stenosis, seizures, scoliosis, long bone dysplasia, sphenoid bone dysplasia, short stature, macrocephaly, and peripheral nerve sheath malignant tumors. Mental retardation is not common (about 5%), while learning disabilities are more common (30-60%).

The diagnosis of NF-2 is based on criteria that were first developed in 1987 by the NIH. The Clinical Care Committee of the National Neurofibromatosis Foundation later revised this in 1997, the criteria of which is seen below (7):

Definite NF-2: Bilateral vestibular schwannomas (VS) or family history of NF-2 (first-degree relative) plus: 1) Unilateral VS (<30 years of age), or 2) Any two of the following: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities.

Presumptive or Probable NF-2: Unilateral VS (<30 years of age) plus at least one of the following: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities. Or multiple meningiomas (two or more) plus unilateral VS (<30 years of age) or one of the following: glioma, schwannoma, juvenile posterior subcapsular lenticular opacities.

The vestibular schwannoma, previously known as the acoustic neuroma, is the hallmark tumor of NF-2. This tumor arises from the vestibular branch of cranial nerve VIII, and is universal in patients with this type of neurofibromatosis (12). Although this tumor arises from the vestibular branch, the patient usually notices hearing problems before vestibular problems (e.g., balance). The average age of onset is 18 to 22 years, although it ranges from 10 years to over 35 years of age. The patient may first present with hearing problems, such as when using the telephone. The onset is gradual, although sometimes it can occur suddenly. Besides tinnitus and deafness, other signs and symptoms include facial weakness, visual problems, and painful peripheral nerve tumors. Children present differently from adults in that they show manifestations not involving cranial nerve VIII. These include spinal cord compression by gliomas or meningiomas, and ophthalmologic problems such as cataracts, strabismus, and amblyopia (7).

Cafe au lait spots can be a sign of neurofibromatosis or a part of other neurocutaneous syndromes. The following is a list of diseases that involve cafe au lait spots:

1. McCune Albright syndrome
2. Tuberous sclerosis
3. Fanconi anemia
4. Bloom syndrome
5. Ataxia telangiectasia
6. Russell-Silver syndrome
7. Multiple lentigines (LEOPARD) syndrome
8. Multiple endocrine neoplasia type 2b
9. Bannayan-Riley-Ruvalcaba syndrome

Solitary cafe au lait spots are commonly seen in the healthy population, although three or more spots can be seen in 0.2 to 0.3% of normal children, and six or more spots in less than 0.1% of healthy children. To suspect NF-1, there should be six or more cafe au lait spots that are larger than 0.5 cm in prepubertal patients, and larger than 1.5 cm in postpubertal patients. These spots are not a major feature

of NF-2, and these patients may have only a few spots present. McCune Albright syndrome includes precocious puberty and multiple endocrine problems. The cafe au lait spots are often large and irregular. It has been compared to having the shape of the coast of Maine, compared to the smooth shape of NF, which is likened to the coast of California.

Tuberous sclerosis (TS) is discussed in a separate chapter. Although cafe au lait spots are not as common as the hypopigmented macules in TS, they can be present. These spots can be seen in 25% of patients with Fanconi anemia, which presents with aplastic anemia, mental retardation, generalized hyperpigmentation, radial ray defects, eye anomalies, and other multiorgan problems. NF patients, unlike Fanconi anemia, do not have anemia. Bloom syndrome is an autosomal recessive disorder that features areas of hypo and hyperpigmentation, prenatal and postnatal growth retardation, thin triangular facies, telangiectatic rash in sun exposed areas, and malignancies (leukemia, breast, and gastrointestinal). Ataxia telangiectasia can also have cafe au lait spots, but probably only in a minority of patients. This disease includes progressive neurodegeneration, bulbar conjunctival telangiectasia, immunodeficiency, and increased risk for malignancies. Russell Silver dwarfism can also have cafe au lait spots but some studies report that it might not be different in frequency to the normal population. This disorder includes prenatal growth retardation, small triangular facies, and short and curved fifth fingers.

The management of a patient with neurofibromatosis should focus on genetic counseling and evaluating for the development of new tumors. The patient should be referred to a neurofibromatosis clinic if one is available, because of the multidisciplinary assistance that can be received. Blood pressure should be obtained at every visit because of the higher risk for hypertension. Those with scoliosis should be referred to an orthopedist for treatment. Learning disabilities can occur and the patient should be evaluated for this annually in terms of his or her academic performance. Dermal neurofibromas can be removed surgically or by laser. Annual eye examinations should be performed annually for the first six years of life, with less frequent examinations thereafter. Prenatal diagnosis is available for NF-1 by amniocentesis or chorionic villus sampling, and can be performed if one of the parents has NF. However, NF is of variable severity, therefore, the value of determining whether a fetus has NF is controversial (9).

The management of NF-2 includes genetic counseling, annual hearing screenings, and surgery for tumors. Because of the risk for deafness, learning sign language and wearing hearing aids should be considered (7).

The prognosis for NF-1 is not a promising one. Throughout life, these individuals develop more lesions, with new types of tumors such as Lisch nodules, neurofibromas, and optic gliomas appearing. A feature of neurofibromatosis is its clinical variability, so it is difficult to determine who will be having severe, debilitating, and disfiguring disease. However, the life expectancy for NF-1 patients is reduced in general, with most deaths occurring in childhood or middle adulthood. Deaths in childhood are usually caused by an intracranial tumor, however, a malignant peripheral nerve sheath tumor, leukemia, or an embryonal tumor can be the cause as well. Sometimes, death can also be due to the growth of a plexiform neurofibroma in the cervical to upper mediastinum region. Deaths in middle adulthood are due to a malignant peripheral nerve sheath tumor or sarcoma from another type of tissue. Other causes are acute hydrocephalus, severe seizures, gastrointestinal hemorrhage, intracranial hemorrhage due to vasculopathy, progressive spinal cord encroachment by plexiform neurofibromas or unstable dysplastic scoliosis, and complications of hypertension due to arterial dysplasia or pheochromocytoma.

NF-2 patients do not fare well either. The average life expectancy is 36 years with death being due to surgically inoperable tumors. These patients also suffer from vision and hearing deterioration, chronic pain from tumors, and loss of ambulation.

We have now identified the gene and gene products for neurofibromatosis. With new discoveries and technologies, gene therapy may be used to treat and prevent this disease in individuals at risk in the near future.

Questions

1. How many cafe au lait spots are needed to diagnose neurofibromatosis? How big do they need to be in prepubertal and postpubertal patients?
2. What is the hallmark tumor in NF-2? How is it manifested in a patient?
3. If you see a patient with cafe au lait spots who you suspect has von Recklinghausen's disease, what tests or evaluations need to be performed?
4. What types of neurofibromas can become malignant?
5. What skin manifestations occur in the newborn period? How about in older children and adults?
6. What is the genetic inheritance pattern for neurofibromatosis? What percentage of cases occur without a family history of NF (sporadic)?
7. What are the eye tumors that you can find on the iris of NF-1 patients called?

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Answers to questions

1. 6 spots. >5 mm in prepubertal and >15 mm in postpubertal patients.
2. Vestibular schwannoma (acoustic neuroma). It is manifested by hearing problems.
3. Blood pressure measurements and eye examinations.
4. Deep nodular neurofibromas and diffuse plexiform neurofibromas.
5. Cafe au lait spots in newborn period. Discrete cutaneous and subcutaneous neurofibromas, axillary freckling in the older patient.
6. Autosomal dominant. 50% occur without a family history.
7. Lisch nodules.

Chapter XVIII.12. Tuberous Sclerosis Complex
Vince K. Yamashiroya, MD

A 10 month old girl presents to the emergency room for tonic-clonic seizures lasting a few minutes. This baby girl is a product of a normal pregnancy and was delivered full-term by normal spontaneous vaginal delivery. There were no postnatal complications and this infant was discharged from the hospital at 48 hours of life. Her history is significant for jerking movements (onset at 5 months of age) described as sudden flexion of the neck, arms, and legs onto the trunk preceded by a cry. Her parents were not too worried about this behavior since the child would return back to normal and they attributed it to colic or "gas". There was no history of fever, coughing, vomiting or diarrhea. She has been gaining weight appropriately and eating normally. She is on solid foods and formula, which the parents prepare correctly. Her immunizations are up to date. She is on no medications and her development has been normal. She is able to sit up, crawl, cruise with both hands, and combines syllables.

Her family history is also unremarkable in that there is no history of seizures, mental retardation, or consanguinity.

Exam: VS T 37.0, P 100, R 26, BP 90/60, O2 sat 100% on RA, weight 9.0 kg (50%ile), length 73 cm (50%tile), HC 44.5 cm (50%tile). She is alert and active in no distress. She is not toxic. She tracks well. She has good bonding with mother. She has multiple small 1-2 cm oval, irregular hypopigmented macules on her trunk and extremities. HEENT is normal. Her neck is supple without lymphadenopathy. Heart, lungs and abdomen are normal. Neuro: She has no facial asymmetry. She moves all her extremities well. There are no focal deficits. She does not exhibit cortical thumbing or scissoring of her lower extremities. She tracks well. She has good head control and is able to support herself on her legs.

In the ER, her work-up includes a head CT scan revealing cortical tubers in the cerebral cortex and multiple subependymal nodules in the lateral ventricles. She is admitted to the floor where an EEG shows "hypsarrhythmia". An echocardiogram and a renal ultrasound are also done showing tumors in both the heart and kidneys. A diagnosis of tuberous sclerosis is made. She is started on ACTH, unfortunately her condition fails to improve and she continues to have intractable seizures in addition to being mentally retarded.

Tuberous sclerosis was probably first described by Friedrich Daniel von Recklinghausen in 1862, when he presented a baby who died "after taking a few breaths". She had pathological findings of tumors bulging from the heart, which Dr. Recklinghausen named "myomata" and described in few words, the brain having "a great number of scleroses." Then in 1880, Désiré-Magloire Bourneville first described the brain of a diseased individual in greater detail, and used the term "tuberous sclerosis of the cerebral convolutions" because of the gross nodular appearance of the brain tumors resembling tubers, or roots of a plant (1).

Over a century later, we know much more about tuberous sclerosis complex (TSC). It is one of the neurocutaneous syndromes because it is thought that TSC is due to a defect in differentiation of the primitive ectoderm, which gives rise to the nervous system and skin. Therefore, it is in the same family of disorders, which includes neurofibromatosis, Sturge-Weber disease, von Hippel-Lindau disease, ataxia telangiectasia, linear nevus syndrome, hypomelanosis of Ito, and incontinentia pigmenti (2). It was also thought to be similar to neurofibromatosis and von Hippel-Lindau disease as being one of the phakomatoses, which is derived from the Greek word phakos, meaning "spot." This "spot" refers to a congenital grouping of nevus cells that is found in several organs and has the potential of enlarging and forming a tumor by cellular proliferation.

TSC is inherited as an autosomal dominant trait like neurofibromatosis; however, at least half of the cases are due to new mutations. The estimated frequency is 1 in 6000, and there is no racial predilection; therefore, we have seen several of these patients in Hawaii. There have been two genes implicated in TSC discovered so far, called TSC1 and TSC2 which are located on chromosomes 9q34 and 16p13 respectively. The TSC1 gene encodes for a protein called hamartin and the TSC2 gene encodes for tuberin. Although these two gene products have been discovered, the diagnosis of TSC is a clinical one and is not dependent on a blood test yet. The complicating feature of TSC is its wide clinical expression. Therefore, one patient could be asymptomatic while another patient could have seizures and severe mental retardation. Although variable expression is a feature of TS, it is doubtful that there is incomplete penetrance, meaning that a person with an autosomal dominant gene defect does not show any signs of the disease (3). This makes genetic counseling very difficult since one cannot predict what the phenotypic expression of the offspring will be, even though the chances of an individual having TSC is 50% given that one of the parents have the dominant allele. Also, because of the variable expression of this disease, it is imperative that in obtaining a family history, one asks if there is a history of mental retardation; seizures; obstructive hydrocephalus; brain or cardiac tumors; cardiac dysrhythmias at an early age; stillbirths (especially with hydrops); kidney, lung, or bone cysts; pulmonary failure; spontaneous pneumothorax; renal angiomyolipomas or failure; fibromatous growths around or under the nails or on gums; enamel pits; retinal phakomas; skin lesions such as hypopigmented macules, facial angiofibroma and shagreen patches; poliosis (premature white hair) or canities (white hairs) of the scalp, lashes, or brows; and iris depigmentation, in addition to recognizing that these signs can be mistaken for vitiligo, refractory acne, or autosomal dominant polycystic kidney disease. However, family history is often insufficient; therefore, family members should be examined for hypopigmented macules (with a Wood's lamp) and brain anomalies by computed tomography. Because

of the possibility for other tumors, ophthalmologic examination, renal radiographic studies, chest radiography, and echocardiogram are often ordered.

TSC is classified as a neurocutaneous syndrome meaning that its manifestations include neurologic and dermatologic features. Vogt proposed a diagnostic triad for TSC in 1908 being mental retardation, seizures, and adenoma sebaceum; however, because of the variable clinical expression, this triad of symptoms may not be present all together, and is therefore not used. Tuberous sclerosis is a multiorgan disease and does not only include the brain pathology; therefore, "tuberous sclerosis complex" may be a better term for this disease (4).

The diagnosis of TSC is still made clinically and as mentioned previously, the identification of TSC1 and TSC2 and their gene products have not changed the way it is diagnosed. The Consensus Conference on TSC by the National Tuberous Sclerosis Association in 1998 categorized major and minor diagnostic features (listed below) for the diagnosis of the tuberous sclerosis complex. A definitive diagnosis of TSC is made by either 2 major features, or 1 major and 2 minor features. Probable TSC is made by 1 major plus 1 minor feature. And possible TSC is made by either 1 major feature or 2 or more minor features (4).

Major Features
1. Facial angiofibromas or forehead plaques
2. Nontraumatic ungual or periungual fibroma
3. Hypomelanotic macules (more than 3)
4. Shagreen patch (connective tissue nevus)
5. Multiple retinal nodular hamartomas
6. Cortical tuber
7. Subependymal nodule
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma, single or multiple
10. Lymphangiomyomatosis
11. Renal angiomyolipoma

Minor Features
1. Multiple randomly distributed pits in dental enamel
2. Hamartomatous rectal polyps
3. Bone cysts
4. Cerebral white matter radial migration lines
5. Gingival fibromas
6. Nonrenal hamartomas
7. Retinal achromic (pale, without color) patch
8. "Confetti" skin lesions
9. Multiple renal cysts

TSC can sometimes present during the first year of life with infantile spasms. In two studies, infantile spasms were the presenting complaint in 69% of patients. Infantile spasms usually begin between the ages of 4 and 8 months, and present with brief symmetrical contractions of the neck, trunk, and extremities, which can either be in flexion or extension, or both. Clusters of seizures may last for minutes with a brief period occurring between each seizure, and may be preceded or followed by a cry. Because of this, the spasms are sometimes mistaken for colic. The spasms have a tendency to occur when the infant is drowsy or upon awakening. Infantile spasms have a very unique pattern on EEG, called hypsarrhythmia, which consists of chaotic, high-voltage, bilateral, asynchronous, slow-wave activity (5).

Perhaps more characteristic of TSC is the development of other types of seizures. The seizures are thought to be due to the cortical tubers or its surrounding cortex that occur in the brain of these patients, although they can sometimes be secondary to cerebral cortex next to a subependymal giant cell astrocytoma. Seizures are the presenting symptom in about 90% of patients with this disease, most of who are children. Although they can occur at all ages, they usually occur in the first year of life. The most common seizure types, besides infantile spasms, are partial simple, partial complex, and partial with secondary generalization (6).

Given that TSC involves hamartomatosis, a condition in which benign tumors form from dysplastic cells that multiply excessively, imaging is extremely important. Because of the CNS manifestations, CT and MRI are essential in the evaluation of a patient suspecting of having TSC, especially if signs of cerebral involvement are present. Cortical tubers, which are most characteristic of TSC, are primarily located in the cerebral cortex and underlying white matter, and are called hamartias, or groups of dysplastic cells that do not grow more rapidly than the other normal cells. They are sometimes calcified, often multiple, and hypomyelinated. Two hamartomatous brain lesions are subependymal nodules and subependymal giant cell tumors. Subependymal nodules are growths that are usually on the outer walls of the lateral ventricles, nearly always next to or within the caudate nucleus. They are generally less than 1 cm and may calcify. They are found in about 80% of patients, and are the single most diagnostic feature by CT scan of TSC. Another unique brain lesion is the subependymal giant cell tumor. These tumors usually lie adjacent to the foramen of Monro and are histologically identical to the subependymal nodules. The difference between the giant cell astrocytomas and subependymal nodules is the propensity for growth in the former. Because of its location, there is a propensity of these tumors to cause hydrocephalus from obstructing the flow of CSF through these foramina (7).

After seizures, mental retardation and other psychiatric problems are also commonly seen in tuberous sclerosis patients. Patients who have never had seizures, infrequent seizures, or seizures after 4 years of age, will most likely have normal intelligence and development. Behavioral and psychiatric problems that are seen in TSC includes ADHD, sleep problems, childhood schizophrenia, and autism.

Ash leaf spots are irregular, hypopigmented macules resembling the leaves of the ash tree (also similar to Hawaiian maile leaves) (8). These lesions occur in the majority of patients with TSC and are often seen at birth, although they can appear months or years later. They appear on the trunk and extremities, number anywhere from 3 to 4, to more than 100, and are usually 1.0 cm or larger. At times, numerous tiny macules are grouped together, resembling confetti, and are usually located in the distal parts of the extremities. Although ash leaf spots appear at birth and may last throughout life, they can become less obvious with time and disappear. These hypomelanotic

macules are best seen with a Wood's lamp or ultraviolet light, since melanin absorbs light in the wavelength of 360 nm, making the macules that are deficient in melanin stand out (9).

Adenoma sebaceum or facial angiofibroma is a pathognomonic finding in TSC and was found in over 80% of patients over 5 years of age in one study. They are tiny red or pink papules with a glistening surface found bilaterally over the cheeks, chin, and nasolabial folds in a butterfly fashion. Larger angiofibromas can occur on the scalp or forehead, and appear as large, flesh-colored plaques that can be soft and doughy to hard. These lesions persist for life.

Another characteristic dermatologic manifestation is the shagreen patch. The word shagreen comes from the French words, peau chagrinee, which mean, "skin with the appearance of untanned leather." This lesion usually appears after the first decade of life and persists throughout life. They are usually found in the lumbosacral area, but sometimes are located elsewhere on the trunk. They are yellowish brown or pink in color, feel like pigskin or an orange peel, and can be few millimeters to over 10 cm in size. They are the second only to ash leaf spots as being the most common lesion in TSC that is found in the trunk.

Ungual fibromas, another characteristic sign of TSC, are flesh colored, or red papules or nodules found on the finger or toe nail bed, with the toes being more common than the fingers, ranging from 1 to 10 mm in size. These fibromas occur more commonly in females, grow back when removed, and appear during or after puberty.

For ophthalmologic lesions, the most common retinal hamartoma is the noncalcified tumor, which appears as a smooth, salmon-gray colored, circular lesion with indistinct borders. These tumors are usually located superficially to a retinal artery and are found in over half of patients with eye involvement. The second type of retinal tumor is the calcified mulberry tumor. Despite the lesions that can occur in the eye, blindness is rare, except in cases where the tumor involves the fovea or optic nerves (10).

Another common tumor is the cardiac rhabdomyoma, which can occur in about 50% of patients. These tumors can occur in any of the four chambers, although it is most commonly located in the left ventricle. Echocardiography is an essential component in the work-up of these individuals (11).

Renal involvement occurs in about 80% of patients with TSC. The lesions include angiomyolipomas, cysts, and renal cell carcinomas. Angiomyolipomas are localized proliferations of blood vessels, smooth muscle and fat. They can be associated with chronic renal failure, with the risk increased if there are also cysts. Cysts can develop in infancy and usually present with severe hypertension due to a mass effect of the cyst into the renal vessels (12).

The differential diagnosis of tuberous sclerosis complex is dependent on the presenting symptom, which in most cases are seizures. There are many causes of seizures, however, it is important to note whether any neurocutaneous stigmata such as ash leaf spots or cafe au lait spots are present since they will be clues that neurocutaneous syndromes like tuberous sclerosis or neurofibromatosis may be the cause. Therefore, a careful skin examination is essential in the evaluation of seizures.

There are many manifestations and degrees of severity of tuberous sclerosis; therefore, management should be aimed at treatment and evaluation of the symptoms. Patients with seizures should have an imaging test such as CT, and an EEG performed to look for anatomical abnormalities or abnormal EEG patterns such as "hypsarrhythmia". If tuberous sclerosis is suspected, the patient should also have an echocardiogram and renal ultrasound or CT done since the chances for cardiac and renal tumors are high. A good funduscopic examination is essential to determine the presence of retinal hamartomas.

The treatment of seizures is difficult because these seizures are often refractory to antiepileptic drugs. The best drug we have available for infantile spasms (also called hypsarrhythmia seizures) in the United States is intramuscular ACTH, however, the drug of choice is vigabatrin because it is safer and more effective. Vigabatrin is an anticonvulsant which inhibits GABA transaminase, which breaks down GABA (an inhibitory neurotransmitter) (13). However, the U.S. Food and Drug Administration has been reluctant to approve it because of its risk of psychosis (about 1-2%), clefts in the myelin sheath of peripheral nerves seen in rodents, and case reports of permanent peripheral vision loss. ACTH can lead to hypertension and other side effects of corticosteroids, such as osteoporosis, weight gain, Cushingoid appearance, avascular necrosis of the femoral head, etc.

Genetic counseling is very important in the management of TSC. A good family history should be obtained in addition to examining the family members for any signs and stigmata of TSC. Since it is autosomal dominant, the chances that an offspring will have this disorder is 50%; however, given the phenotypic variability of this disease, predicting the outcome of the couple's future children can be difficult. For example, because less than 50% of individuals with tuberous sclerosis will have mental retardation, the couple should be told that their offspring will have about a 25% chance of being mentally retarded. Other alternatives for having children should also be discussed; those being adoption, artificial insemination with donor sperm, and in vitro fertilization with a donor egg. If there is a negative family history and sporadic disease is likely, then the chances for future offspring having the disease is probably less than 2%, although one of the parents could still carry the gene and not thought of having the disease since its expression may be very mild. Prenatal diagnosis may be possible as early as 22 to 25 weeks by detecting the presence of cardiac or brain tumors; however, this is not always possible. If it is known that this family has a TSC1 or TSC2 gene mutation, then it may be possible to detect this mutation in the fetus through chorionic villus sampling.

The outcome of tuberous sclerosis complex is variable, depending on the severity of the disease. Some individuals may have a normal lifespan and not know that they have the disease, whereas, others could succumb to a lifetime of intractable seizures, mental retardation, or the development of other hamartomas throughout their adult life leading to new problems.

I would like to thank Dr. Robert Bart for reviewing this chapter and his useful comments and suggestions.

Questions

1. How is tuberous sclerosis complex inherited?
2. What percentage of TSC is sporadic (due to new mutations)?
3. Name three dermatological features of TSC. At what ages do each of these lesions occur?
4. What is the treatment of choice for infantile spasms that is approved by the FDA?
5. What is the EEG pattern of infantile spasms?
6. If a patient is diagnosed with TSC by computed tomography of the brain, what other tests must be done in the work-up?

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Answers to questions
1. Autosomal dominant.
2. 50%.
3. Ash leaf spots (birth), adenoma sebaceum or facial angiofibroma (5 years old), shagreen patch (after 10 years old).
4. ACTH.
5. Hypsarrhythmia.
6. Echocardiogram and renal ultrasound.

Chapter XVIII.13. Head Trauma and Hemorrhage
Floyd S. Ota, MD

Two days ago, this 6 month old male infant was sitting in an infant carrier which was placed on top of a stroller. The carrier accidentally fell approximately 3 feet onto the ground. He hit his head on the plastic portion of the car seat. There was an immediate cry and no loss of consciousness. His behavior, activity, and feeding pattern were reported as normal. Two days later (today) his mother notes a boggy swelling in the right temporal area of the head and because of this, she brought him to the emergency room for evaluation. He continues to have normal activity and no vomiting.

He has been previously healthy. There is no history of substance use, or child protective services (CPS) involvement in the family.

Exam: VS T 36.9, P 120, R 18, BP 92/50, oxygen saturation 100% in room air. Height, weight and head circumference at the 25th to 50th percentiles. He is alert, active, easily arousable on exam and clean in appearance. He has a 9 by 7 cm swelling over the right temporal/parietal region that is soft, possibly tender, with no palpable bony deformity. No lacerations or wounds are noted. His anterior fontanel is soft and flat. Pupils are 3 mm bilaterally and reactive to light. EOMs are conjugate. There is no hemotympanum, no nasal discharge, and his mucus membranes are moist. His heart, lung, and abdomen exams are normal. Neurologic and extremity exams are normal.

A head CT scan shows a subgaleal hematoma (hematoma under the aponeurosis of Galen), a non-depressed linear skull fracture, and a normal brain. He is discharged home to the care of his parents. He followed up with his pediatrician the next day without sequelae.

Head injuries are the most common cause of traumatic death in children. Head injuries result in about 600,000 visits to the emergency department, and 250,000 hospitalizations annually (1,2). The main causes of head injuries in children overall in descending order are falls, motor vehicle crashes, pedestrian accidents, bicycle injuries, and other injuries (e.g., sports injuries, assault, and non-accidental trauma) (2). Motor vehicle accidents are the most common cause of traumatic death due to head injuries. The diagnostic dilemma for treating head injured children lies in identifying those patients who require more acute attention, and differentiating them from stable patients.

Younger children are at higher risk for sustaining serious head injury. Anatomical considerations that predispose the younger child to head injuries are a large head to body ratio, a relatively weak neck, a thinner skull, and a larger subarachnoid space in which the brain can move freely (2). The pathophysiology of head injuries can be subdivided into two types. The injury directly caused by the mechanical force of the trauma is called primary injury. This type of injury is due to shear force, direct contact, and tissue penetration. Secondary injury is created by the body's response to the primary insult. In secondary injury excitatory neuropeptides, cytokines, free radicals, metabolic and oxygenation insufficiencies cause further tissue damage. Little can be done about primary injury once it has occurred. However, medical management theoretically attempts to minimize the damage caused by secondary injury.

It is important to realize that unlike injuries to other parts of the body, injury to the brain occurs within a confined volume, the intracranial space. The intracranial space is made up of three components; brain volume (90%), blood volume (5%) and cerebral spinal

fluid volume (5%). Initially, as the brain swells in response to injury, the increase in brain volume is accommodated by a reduction of cerebral spinal fluid volume, and then blood volume. However, in the finite space of the calvarium, the mass effect caused by acute brain edema and hemorrhage may reach a point at which this volume can no longer be accommodated. Thus, at some point, even the smallest increase in brain volume or hemorrhage produces an exponential increase in intracranial pressure (ICP), at which point, brain perfusion is seriously compromised. This dramatic rise in pressure impedes cerebral perfusion and results in the herniation of brain tissue across the tentorium, falx or through the foramen magnum causing significant morbidity and often death. Intracranial hypertension, or elevated intracranial pressure is harmful as it can decrease cerebral perfusion, inciting further hypoxia and cell death. This relationship between ICP, mean arterial pressure (MAP), and cerebral perfusion pressure (CPP) can be appreciated by the equation CPP=MAP-ICP (1). In normal children ICP is <20 mm Hg, and MAP is 70-80 mm Hg, which provides a normal CPP ranging from 50-60 mm Hg (1). Thus, accordingly an increase in ICP, or decrease in MAP can decrease blood flow into the brain. When CPP is <40 mm Hg, ischemia occurs as proper cerebral blood flow (CBF) cannot be maintained (1). This simplified equation attempts to explain a very complicated pathophysiologic process. Controlled by chemical mediators that produce vasoconstriction and vasodilatation of the blood vessels, CBF is constantly changing to meet the brain's metabolic demands. The most potent chemical mediator is the arterial partial pressure of carbon dioxide (pCO2), which is directly proportional to CBF. The arterial partial pressure of oxygen (pO2) is indirectly proportional to CBF, but it is not as potent a vasoactive mediator as pCO2. In the acute management of the patient with a severe head injury, these values are manipulated via intubation and mechanical ventilation to maximize CPP.

The initial clinical assessment is extremely important in determining the clinical management of a victim with head trauma. The primary survey should begin with the standard ABCs of basic life support and a focused physical exam looking for concurrent life-threatening injuries involving the chest, central nervous system, pelvis, and abdomen. All the while, the patient's mental status is closely monitored. The Glasgow Coma Scale (GCS) has been found to be helpful for this purpose (1). The GCS is a clinical rating scale developed based the patient's clinical assessment in three categories; motor, verbal, and eye opening response. The GCS scale ranges from 3-15. The GCS scale is as follows:

Motor response: 6=normal spontaneous movements, 5=withdraws to touch, 4=withdraws to pain, 3=abnormal extension (decorticate rigidity), 2=abnormal flexion (decerebrate rigidity), 1=none.

Verbal response: 5=oriented, 4=confused, 3=inappropriate words, 2=nonspecific sounds, 1=none.

Eye opening response: 4=spontaneous, 3=to speech, 2=to pain, 1=none (1).

A modified Glasgow Coma Scale for infants was created for pre-verbal children. The GCS is not useful in ruling out serious brain injuries such as hemorrhages since many patients with brain hemorrhages have GCS scores >13, and some even have 15 (normal) GCS scores. Once the patient is clinically stable, a more detailed secondary survey can be carried out.

The majority of head injuries (90%) fall into the minor category. If the head injury has been determined to be mild, a history looking for symptoms of possible intracranial injury should be elicited. This would include questions pertaining to loss of consciousness, headache, amnesia, seizures, nausea, vomiting, or focal neurological defects. Minor head trauma is a difficult clinical dilemma, and multiple studies have shown that no single symptom consistently identifies the presence of an intracranial injury (ICI) in children (3,4). Two prospective studies found that the following clinical findings were commonly associated with intracranial injury in children with minor head trauma: focal neurological deficits, loss of consciousness, amnesia, a GCS less than 15, and altered mental status (3,5). It turns out that a 14 GCS is close to 15, but there is a substantially higher risk of serious head injury if the GCS is 14 compared to 15. Thus, if these clinical findings are present during the assessment, then computed tomography (CT) scanning is indicated. Computed tomography scanning of the head is the diagnostic procedure of choice to determine the presence of acute intracranial injury (6). CT scanning is often easily accessible and a very good test to screen for the presence of acute bleeding and brain swelling. Unfortunately, some children require sedation to perform a CT scan, and thus the risks and benefits of procedural sedation must be weighed. However, the need for procedural sedation is declining with the advanced technology of faster spiral CT scanners. Skull x-rays have a limited role in children with head injuries, since they do not identify intracranial injury. However, these images may be helpful when CT scanning is not available. Plain x-rays can detect a skull fracture, and the presence of a skull fracture was found to be helpful with predicting the presence of intracranial injury (5). However, a normal skull series does not rule out a brain injury. Magnetic resonance imaging has no role in the initial evaluation of an acute head injury since it is time consuming, expensive, and not usually readily available. In minor head injuries, management is almost always observation and parental education. Hospitalization is utilized if there is concern about proper follow up, since most complications will occur within the first 24 hours following the injury (6). Parents should be instructed on what signs to look for and when to return for further care. Separate practice guidelines have been recommended for the management of minor head injuries in children ages 2-20 years and <2 years of age by the American Academy of Pediatrics (6,7).

Skull fractures can occur with even mild trauma. Infants are especially susceptible to linear skull fractures, because of their thinner skull. Half of skull fractures occur from a fall from a height of 4-5 feet, and 70% involve the parietal bone (1). Very often superficial scalp lacerations and hematomas are also present on exam. It is important to mention that in infants, scalp lacerations can cause significant bleeding if left unrecognized. The presence of scalp hematoma has a 95% association with finding an underlying linear skull fracture in infants (8). Thus, diagnostic imaging is recommended for any infant with an obvious scalp hematoma. (7,8). Despite the fact that only close observation is all that is required for a linear skull fracture, proper follow up is important. Rarely, a growing skull fracture can develop. This occurs when a portion of the meninges herniates through the fracture line and does not allow for proper healing. A fluid collection cyst can be produced by the pinched meninges, which is called a leptomeningeal cyst. Leptomeningeal cysts (hence, growing skull fractures) are rare complications, but the clinician should still look for them during follow up weeks after a skull fracture is found.

A subgaleal hematoma will often form around a parietal skull fracture. It is common for these to present several days after the head trauma incident. The infant or young child strikes his/her head during a fall. If a skull fracture is sustained, without a brain injury, the child will appear to be alert and active without signs of brain injury. Bleeding from the skull fracture collects in the subgaleal layer of the scalp. It is initially tense, but over the next few days as the hematoma begins resorption, the hematoma becomes very soft, which is often alarming to parents, prompting them to bring the child to a physician. Skull radiographs frequently identify a small linear fracture beneath the subgaleal hematoma which does not require further diagnostic or therapeutic intervention if the child is doing well clinically. However, radiographs occasionally demonstrate large fractures, comminuted fractures, or multiple fractures which suggest more serious injury and/or non-accidental injury.

A skull fracture that is pushed in a distance equivalent to the thickness of the skull table is called a depressed skull fracture. This is a neurosurgical emergency and must be corrected expeditiously. Lastly, basilar skull fractures (BSF) may occur from head trauma, and can be diagnosed by clinical exam. Physical exam findings associated with a BSF include: blood in the mastoid air space (Battle's sign which is bruising over the mastoid process), blood collection in the periorbital space (Raccoon eyes), hemotympanum, and CSF

rhinorrhea. BSF were found to be associated with the presence of ICI (5). Thus, radiographic imaging should be performed if these clinical signs are found. A small increase in the risk for meningitis is associated with a BSF due to the break in protective covering that the meninges provide. This risk is small and prophylactic antibiotics are not routinely recommended. However, this needs to be considered in the febrile child with a recent history of a BSF during follow up care.

The most mild type of brain injury is a concussion. A concussion is defined as, "a trauma induced alteration of mental status that may or may not involve a loss of consciousness" (1). Very often, confusion and/or amnesia may accompany the event. In concussions, CT scans are normal and close observation is all that is required. The "Second Impact Syndrome," is characterized by rapid death due to a second concussion prior to a return to baseline functioning after an initial one. Sudden death is thought to occur due to a rapid rise in ICP from local vasospasm and edema (9). This has been reported to occur in adolescent athletes in contact sports, and the appropriate time to return to activity after sustaining a concussion is under much debate. Practice guidelines for the return of activity after sustaining a concussion have been recommended in the literature (10).

An epidural hematoma (EDH) can develop if blood collects in the potential space between the dura and the inner table of the skull. Very often the blood is arterial originating from the middle meningeal artery in association with a parietal skull fracture. However, in younger children, 20% of epidural hematomas are due to venous blood (1). The classic clinical coarse is that of a child who sustains a head injury and may have been rendered unconscious. He may then have the "classic" lucid interval at which time he may be able to interact with the examiner. This is because, the initial brain injury itself is only a concussion. Subsequent middle meningeal bleeding causing the hematoma results in ensuing decompensation from the expanding blood collection, causing increased intracranial pressure and a reduction in cerebral perfusion (a secondary injury). An epidural hematoma is best diagnosed by CT scan, which will show a lenticular (football shaped) hyperdense (white) hemorrhage along the skull table. EDH can cause a significant increase in ICP, illustrated by a midline shift and small ventricles on CT scan. This is a neurosurgical emergency, and craniotomy with evacuation of the hematoma can be life saving. If neurosurgical intervention is early and successful, EDH has a good prognosis since the initial brain injury was only a concussion in most instances (i.e., the brain itself is not significantly injured in an EDH, since the bleeding originates from outside the brain parenchyma).

A subdural hematoma (SDH) is the accumulation of blood in the subdural space. This is most often due to venous blood from the bridging veins that traverse this space. Very often a SDH is created by acceleration-deceleration injury in which the brain parenchyma is damaged from the surface of the calvarium. CT scanning of these lesions will show a crescent shaped hyperdense (white) hemorrhage. The majority of SDH are managed medically, and observation with supportive care is all that is required. This is usually not a neurosurgical emergency, since evacuation of the clot will not usually reverse the significant primary damage inflicted on the brain parenchyma. However, neurosurgical intervention may be warranted when a significant mass effect is present, and the patient would benefit from an acute reduction in ICP. When a child presents with unexplained vomiting, lethargy, and/or head trauma, non-accidental injury must be included in the differential diagnosis. Especially when subdural hematomas are found, the possibility for child abuse must be explored. Associated findings of non-accidental trauma are failure to thrive, retinal hemorrhages, intra-abdominal injuries, and various fractures of different ages. In one retrospective review, cases of acute head injury caused by child abuse were often initially misdiagnosed if the patient was well appearing, Caucasian, and living with both biological parents (11). Thus, the examining clinician should have a low threshold to perform a skeletal survey and attain ophthalmology consultation for suspicious cases of head injuries.

This type of acute subdural hematoma is very different from the type of subacute subdural hematoma found in the elderly. Acute subdural hematoma is associated with substantial brain parenchymal injury. Subacute subdural hematoma in the elderly results from a slow bleed from bridging brains often due to minor head trauma. As the hematoma expands, ICP increases and cerebral perfusion is compromised. If the hematoma is identified and evacuated early, the brain is preserved with little injury. The difference between acute subdural hematoma (usually a poor prognosis) should be contrasted with subacute subdural in the elderly (usually a good prognosis). The latter is more similar to an epidural hematoma (usually a good prognosis as well).

The concept of primary versus secondary injury is important in understanding the prognosis. Most epidural hematomas have mild primary injury, but have the potential for severe secondary ischemic injury if failure to evacuate the hematoma in a timely evacuation leads to excessive ICP increase and brain ischemia/infarction. Compare this to an acute subdural in which case, there is substantial primary brain injury (damage) which cannot be reversed with evacuation of the hematoma.

Sometimes a subarachnoid hematoma and an intracerebral contusion can accompany a subdural hematoma. Subarachnoid blood can be distributed widely throughout the subarachnoid space, and its symptoms can sometimes mimic meningitis. On CT scan hyperdense blood collections are found along the falx, and in the basilar cisterns. Intracerebral contusions are actual injury within the brain parenchyma. Due to tissue edema, these lesions are at high risk for producing a mass effect and increased ICP. In this type of injury, the GCS is often low, and focal neurologic symptoms, loss of consciousness (LOC), and visual changes are often present. CT scan shows a mixture of hypo and hyper dense lesions within the brain parenchyma. Secondary injury may further complicate the clinical picture by producing infarcts due to local vasospasm. Medical and neurosurgical management are often required, and the prognosis is usually poor.

In moderate to severe head injuries, medical and surgical management is aggressive and complex. Patients often present in an obtunded or combative state. Late clinical findings include unequal and non-reactive pupils, focal neurologic findings, abnormal posturing, and Cushing's triad (hypertension, bradycardia, and irregular respirations). These clinical findings are usually indicative of severe injury and probable brain herniation. These clinical signs require expeditious medical management, and close monitoring in the intensive care unit. Expeditious CT scanning to determine the extent of brain injury is required. Neurosurgical consultation is required because the only way to accurately access and monitor ICP is to measure it with a direct device such a Richmond bolt or a ventriculostomy. This device, placed by the neurosurgeon, can directly monitor acute changes in ICP. The targeted value for adequate CPP is an ICP <20 mm Hg in the presence of a normal systemic arterial blood pressure. The two physiologic parameters that must be avoided are hypoxia and hypotension. The brain is an obligate aerobic organ and systemic hypoxia leads to increased CNS morbidity. Furthermore, maintaining adequate MAP is critical to maintaining proper CPP.

Monitoring and maintaining the intravascular volume status is crucial. Intravascular volume may be decreased due to capillary leak, an acute bleeding process, or overzealous use of hyperosmotic agents. Very often, vasopressor agents such as dopamine, dobutamine, or epinephrine may be required to maintain proper MAP. The head of the bed should be elevated to 30 degrees to facilitate venous drainage. Sedation and analgesia may aid to decrease dramatic shifts in ICP due to generalized motor activity and anxiety. If these pharmacological interventions fail to adequately minimize changes in ICP, paralytic agents may also be added. If the patient has seizure activity, benzodiazepines or fosphenytoin can be used. Fosphenytoin for seizure prophylaxis may be indicated in the presence of an obvious parenchymal injury. Manipulation of pCO_2 and pO_2 values via intubation and mechanical ventilation may be useful to optimize CPP. However, this is controversial and recommendations are evolving. While moderate hyperventilation was an accepted treatment modality

(with the targeted pCO2 in the 30-35 mmHg range) to reduce ICP, this is controversial since it may reduce net cerebral perfusion by vasoconstricting the cerebral arteries. Perhaps hyperventilation should be reserved for impending brain herniation only.

Osmotic agents such as mannitol or 3% saline are given intravenously to achieve a hyperosmolar intravascular compartment. The hyperosmolarity of the intravascular compartment draws free-water from the interstitial space potentially lowering intracranial pressure and thus improving cerebral blood flow (1,12). Serum electrolytes, and serum osmolarity must be closely monitored. Hyponatremia can result from the inappropriate release of anti-diuretic hormone (SIADH), and hypernatremia may result from diabetes insipidus, dehydration and osmotic diuresis due to the use of hyperosmolar medications. Mannitol and hyperventilation have not been shown to be of clear benefit in the long-term management of increased ICP, and their benefits appear to be primarily helpful in the acute setting dealing with impending brain herniation (1). Despite aggressive attempts at medical management, severe head injuries may continue to progress to a level of refractory intracranial hypertension leading to significant morbidity and/or death.

The prognosis for minor head injuries is very good. Minor effects of the injury that may persist include headache, concentration problems, and hesitation to return to normal activities. These typically resolve and the patient will return to baseline functioning with time (13). For children who survive major head injuries, significant morbidity is common. However, when compared with adults, children with a GCS of <8 often have better outcomes (12). Intensive rehabilitation therapy may be required long after hospitalization and the acute phase is complete. Prognosis may be poor, and for some, a persistent vegetative state may be the result. Head injuries are a major cause of morbidity and mortality in children, and only through primary injury prevention will this problem be decreased.

Questions

1. True/False: Epidural hematomas have a crescent shaped mass on CT scan
2. True/False: Epidural hematomas are mostly produced by venous blood.
3. True/False: The prognosis for epidural and subdural hematomas are about the same as long as the hematomas have been evacuated early.
4. True/False: Since epidural hematoma is always a neurosurgical emergency and subdural hematoma is less often a neurosurgical emergency, epidural hematomas are more serious (i.e., the prognosis is poorer) than subdural hematoma.
5. True/False: Infants are at low risk for having intracranial injuries.
6. True/False: Hypotension and hypoxia are two monitoring parameters that are extremely important to avoid in a child with a moderate to severe head injury.
7. True/False: The equation to calculate cerebral perfusion pressure is: CPP=MAP-ICP.
8. True/False: Hypernatremia can occur secondary to inappropriate anti-diuretic hormone release in moderate to severe head injuries.
9. True/False: A 4 year old male child fell and hit his head on the carpet about 5 hours ago. There is no reported history of loss of consciousness or vomiting. His PE is normal, and he is acting appropriately at the time of the visit. A CT scan should be ordered to assess this child for intracranial injury even though the risk of serious injury is remote.
10. True/False: A patient has a GCS of 9 if he can open his eyes to a noxious stimuli, has inappropriate speech, and flexes his extremities to pain.

Related x-rays

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Answers to questions

1. False. Epidural hematomas are a neurosurgical emergency and have a lenticular (lens or football shaped, also called biconvex) shape on CT scan.
2. False. Only 20% of epidural hematomas are produced by venous blood in children.
3. False. Acute subdural hematoma is associated with substantial brain parenchymal injury so its prognosis is poor compared to epidural hematoma.
4. False. Epidural hematoma is a neurosurgical emergency because its prognosis is dramatically better with early evacuation, while subdural hematoma is less of an emergency because the prognosis is already poor even with hematoma evacuation.
5. False. Infants are at higher risk for sustaining serious head injury. Anatomical considerations that predispose the younger child to head injuries are a large head to body ratio, a relatively weak neck, a thinner skull, and a larger subarachnoid space in which the brain can move freely.
6. True.
7. True.
8. False. Hyponatremia occurs with SIADH. Free-water is retained in the collecting tubules due to anti-diuretic hormone causing a dilutional effect of the serum sodium. Hypernatremia is usually caused by the use of hyperosmotic agents such as mannitol or diabetes insipidus.
9. False. In well appearing children 2-18 years of age with no loss of consciousness and a normal neurological exam, no imaging studies are required. Close observation and parental education is all that is needed (6).
10. True. GCS=9: motor=4, verbal=3, and eye opening=2.

Chapter XVIII.14. Muscular Dystrophy

Vince K. Yamashiroya, MD

In neurology clinic, your next patient is a five year old boy who was referred by his pediatrician because of an abnormal gait. He was adopted from another country about a year ago, and his adopting parents have noticed that he is clumsy when he runs where he falls often. He runs on his tiptoes, which has occurred since they started taking care of him. Otherwise, he has no other problems. He is doing well in kindergarten despite his language difficulty. His teacher notes that he has trouble getting up from a sitting position at school. His parents deny that he has chronic fevers, leg pain, weight loss, seizures, skin rash, urinary or bowel incontinence, or frequent colds.

His past medical history, developmental history, family history, and birth history are unknown. His immunizations are up-to-date and his PPD this year has been negative.

Exam: His vital signs are normal. His height, weight and head circumference are at the 50th percentile. He is alert, active, shy, well-nourished and slim in no distress. His skin shows no neurocutaneous stigmata. His head is normocephalic and atraumatic. His pupils are equal, round, reactive to light. No nystagmus is evident. His fundi are normal with sharp disk margins. His TMs are clear. His throat is normal with a uvula midline. His lungs, heart, and abdomen are normal. His back shows no sacral dimples.

Neurologic exam: A standard cranial nerve exam reveals no deficits. His strength is +4/5 in his deltoids, knee flexors and extensors; +5/5 in his biceps and triceps. His calves are visibly enlarged with a firm, rubbery feeling. He gets up to a standing position using a Gowers' maneuver. No dysdiadochokinesia. Negative Romberg sign. Sensation to light touch is intact. His reflexes are +2/4 in his biceps, triceps, brachioradialis, patella and ankle. His plantar reflex is downgoing (negative Babinski sign). No clonus is elicited. Normal anal wink and abdominal reflexes are present. His gait is best described as a wide based waddling. When running, he tends to run on his toes. He is unable to jump.

You have a suspicion of what he might have, and send off some blood tests and make an arrangement for a muscle biopsy to be performed.

Muscular dystrophy is a term used to describe a primary myopathy that is genetically acquired, is progressive, and is characterized by death and degeneration of various muscle fibers during different periods of the disease. The word dystrophy means abnormal growth, being derived from the Greek word, trophy, meaning nourishment. Therefore, muscular dystrophy can be thought of as an abnormal growth of muscle (1). Although there are many different types of muscular dystrophies, the most well known of them is Duchenne muscular dystrophy (DMD), which is the most common type of muscular dystrophy occurring in childhood.

The inheritance pattern for DMD muscular dystrophy is X-linked recessive. Therefore only males express the disease, with females being carriers. If a female were a carrier, then according to Mendelian genetics, she would have a 50% chance of having an affected son, and a 50% chance of having a daughter who is a carrier. Although family history is usually positive, there is a high rate of spontaneous mutations; about one-third of all cases of DMD are sporadic or new mutations (2).

There are several different types of muscular dystrophies, each with different modes of inheritance, chromosome gene locations and products, and presentations. The types of muscular dystrophy and modes of inheritance are listed below:

1. Duchenne muscular dystrophy (X-linked recessive)
2. Becker muscular dystrophy (X-linked recessive)
3. Myotonic dystrophy (autosomal dominant-expansion of unstable CTG trinucleotide DNA sequence) and congenital myotonic dystrophy (maternally transmitted)
4. Congenital muscular dystrophy (autosomal recessive)
5. Limb girdle muscular dystrophy (autosomal dominant or recessive)
6. Facioscapulohumeral dystrophy (autosomal dominant)
7. Emery-Dreifuss muscular dystrophy (X-linked recessive)

The incidence of Duchenne and Becker muscular dystrophy is 1 in 3,500 male births. Myotonic dystrophy is the most common dystrophy presenting in adulthood, with an incidence in all age groups being 13.5 per 100,000. The incidences of the other types of muscular dystrophies including facioscapulohumeral dystrophy, limb-girdle dystrophy, and congenital muscular dystrophy, are less common then the other muscular dystrophies (2).

When someone mentions muscular dystrophy, we think of Duchenne muscular dystrophy (DMD) since this is the most common of the muscular dystrophies. Therefore, this chapter will focus on the clinical presentation and diagnosis of DMD. The underlying problem in DMD is abnormal or absent dystrophin production. In normal individuals, there is very little dystrophin; however, in DMD patients, this protein is absent or nonfunctional. Although it is known that dystrophin is a cytoskeletal protein, the exact mechanism whereby the absence of this protein leads to muscle degeneration and necrosis is not clear. Dystrophin is transcribed from a gene located in the Xp21 locus. About 70% of cases are due to a gene deletion, 5-10% are due to gene duplications, and the remaining 20-25% are due to point mutations (3).

Duchenne muscular dystrophy usually presents insidiously and after several years of age. The first sign is usually a delay in learning to walk. Normal children usually start walking on the average about 12 months of age; however, in DMD, 56% start walking at 18 months of age, and about 25% learn how to walk after 2 years of age. An inability to run properly is a hallmark sign and appears to be present in almost all cases. Other early signs are a waddling gait, walking unsteadily with frequent falling, walking on toes, and difficulty at climbing stairs. Almost all patients show signs of this disease by 5 years of age, although occasionally, this disease can present as late as 8 to 9 years of age. Another early sign is pseudohypertrophy of the calf muscles. The calf muscles feel firm or woody, in addition to being enlarged. The pseudohypertrophy is due to excessive amounts of adipose and connective tissue secondary to muscle necrosis and destruction from the lack of dystrophin. Despite its size, the muscles are weak. In addition to the calves, other muscles where pseudohypertrophy can be present are masseters, deltoids, serratus anterior, and quadriceps. In general, the pattern of muscle weakness is lower extremities and proximal muscles first, and upper extremities and distal muscles later. This pattern of muscle weakness leads to several clinical symptoms. One is the waddling gait that is seen, which is due to weakness of the gluteus medius and minimus muscles. Another is the lumbar lordosis during walking, which is caused by weakness in the gluteus maximus muscle. Because of an imbalance between the plantar and dorsiflexors, these patients also walk on their toes. After age 4 to 5 years, the Gowers' maneuver can be observed. A positive sign is seen when a child climbs up on his thighs in order to extend his hips and push up his trunk when going from a sitting to standing position. This is due to weakness of the knee and hip extensors. By age 4 years, there is weakness of the pectoral girdle muscles in that the child slides through the examiner's arms when grasped around the chest and is pulled up. Winging of the scapulae can be seen later. Although there is no pain, sometimes children will complain of muscle cramping and stiffness, especially in the calves (4).

The muscle disease is progressive and these patients are usually wheelchair bound before 13 years of age. After the loss in ambulation, equinovarus deformities of the feet and scoliosis develop rapidly. Weakness of the intercostal muscles causes a progressive restrictive respiratory disease to occur leading to nocturnal hypoventilation in the late teens to early 20s. Later, respiratory failure occurs, requiring ventilator support. Patients start to become symptomatic from progressive cardiomyopathies around their teen years, although EKG changes are seen in the early stages of the disease.

Not only does this disease affect muscle, but the central nervous system as well. About 30% of affected boys have lower intelligence quotients, especially in the verbal subtests, although boys having normal intelligence have been reported. Also emotional problems appear higher than in other disorders. The exact mechanism for the lower intelligence and emotional problems is not known; although it is known that dystrophin is normally located in the cortical synapses, and its absence might account for the CNS abnormalities. Seizures and visual and hearing problems are not present in DMD (5).

A similar entity to DMD is Becker muscular dystrophy. This type of muscular dystrophy is also due to mutation of the dystrophin gene, but instead of having a nonfunctional or absent protein product, the dystrophin itself is defective but still partially active. Therefore, these patients have milder forms of muscle weakness, and they usually present later compared to DMD. Progression is also much slower, and these patients may be ambulatory until 16 years of age or older. Cardiac problems may be severe. About 15% of patients younger than 16 years have clinically significant cardiomyopathy, and about 75% of individuals have that problem after age 40 years. Affected patients may live into late adulthood, compared to patients with DMD who die much earlier (2).

Myotonic muscular dystrophy is not due to dystrophin but to an abnormal protein kinase due to an expansion of an unstable trinucleotide repeat in chromosome 9. This disease is characterized by an older age of onset, facial weakness and greater distal muscle weakness, cardiac muscle involvement leading to arrhythmias, cataracts, and endocrine problems (such as diabetes, testicular atrophy, and menstrual irregularities).

Another type of myotonic muscular dystrophy, congenital myotonic dystrophy, is transmitted maternally and is manifested by marked hypotonia in the infant, leading to early death usually due to respiratory insufficiency. If this type of dystrophy is suspected, the mother should be tested for myotonia (2). Congenital muscular dystrophy presents with hypotonia and weakness at birth. There may also be joint contractures, respiratory and swallowing difficulties.

There are some types of congenital muscular dystrophies, such as Fukuyama type, muscle-eye-brain disease, and Walker-Warburg syndrome, which have mental retardation, seizures, hydrocephalus, and structural brain and eye abnormalities. These are autosomal recessive (2).

Limb-girdle dystrophy is a heterogeneous disorder involving several different gene loci. It can be autosomal recessive or dominant (2).

Facioscapulohumeral muscular dystrophy usually presents in late childhood to early adolescence with facial weakness, and weakness of the scapulohumeral muscles. Deltoid muscle strength is spared. It is autosomal dominant (2).

DMD can be suspected clinically; however, there are several tests that can greatly assist in its diagnosis. Serum creatine phosphokinase (CPK or CK) is an enzyme present in muscle, and when there is damage in the muscle cells, CPK is released. Therefore, CPK is highly elevated in DMD, commonly 50 to 100 times normal values in Duchenne and Becker muscular dystrophies (15,000-35,000 IU/L). CPK is usually highest in the early stages of the disease, but then decreases with progression. CPK is not specific for muscular dystrophy. It may also be elevated in spinal muscular atrophy, normal vaginal delivery, acute hypoxic-ischemic cerebral injury, intramuscular injections, muscle trauma, and recent vigorous exercise. Other lysosomal enzymes present in muscle, such aldolase and aspartate aminotransferase are also elevated in muscular dystrophy; however, they are also nonspecific (6).

Electromyography (EMG) may identify a myopathic process, but it is not specific for muscular dystrophy and plays a minor role in its diagnosis. The EMG shows low-amplitude, short-duration polyphasic motor unit action potentials in this disease.

A specific test using molecular genetic techniques can be performed using a blood sample in which the identification of specific gene deletions or mutations is done by PCR. This has obviated the need for muscle biopsies since deletions in the Xp21 gene can be identified to confirm the presence of Duchenne and Becker muscular dystrophy in two thirds of the cases (2). The other cases that are not diagnosed by PCR can be confirmed by the dystrophin immunocytochemistry test on muscle biopsies.

Muscle biopsy is probably very helpful and specific for Duchenne and Becker muscular dystrophy, in addition to other types of muscular dystrophies. Muscle degeneration and regeneration and connective tissue proliferation are present. Staining for dystrophin and other associated proteins through specialized immunocytochemical techniques can be done. Cardiomyopathy can be screened for using chest radiographs, EKG, or echocardiography.

There is a myriad of diagnoses possible for weakness; however, the neurologist is concerned about where the lesion causing the weakness is. The problem can be in the upper motor neurons, peripheral nerves, neuromuscular junctions, or in the muscles themselves. The history and examination can point to the cause of weakness being due to the muscles, and not to other parts of the nervous system. Clues include intact ankle reflexes without clonus or hyperreflexia, no loss of sensation, and pseudohypertrophy. There are several diseases that affect muscles. Myositis is one, although the muscles are tender in this group of diseases. Although dermatomyositis can also present insidiously with a positive Gowers' maneuver, and elevated aldolase and CPK, there are also rheumatologic signs such as a heliotrope rash on the eyelids, rash on sun-exposed areas, and Gottron papules, which muscular dystrophies lack. Some types of spinal muscular atrophies (SMA), such as Werdnig-Hoffman (type 1) and type 2, can be easily differentiated from DMD because these diseases present at a much earlier age with marked hypotonia and weakness, in addition to the presence of fasciculations and a normal to slightly elevated CPK level. Type 3 SMA (or Kugelberg-Welander disease), might be confused with DMD because of its presentation later on in childhood and its pattern of muscle weakness being mainly in the proximal muscles. However, Kugelberg-Welander disease, like the other SMA's, lacks pseudohypertrophy of the calf muscles, muscle fasciculations are present, and deep tendon reflexes are absent. Another differentiating sign is the presence of minipolymyoclonus, which is a fine tremor in the outstretched hands, which is present in the SMA's but absent in the muscular dystrophies (7). Lastly, muscle immunocytochemistry for dystrophin and PCR for Xp21 gene deletions should be able to confirm the diagnosis for Duchenne and Becker muscular dystrophies.

Sadly, there is no definitive treatment for Duchenne muscular dystrophy. Supportive care includes daily passive stretching of joint contractures, night splints, bracing if there is loss of ambulation, orthopedic surgery (including surgical tendon releases and surgery for scoliosis), and ventilatory support measures. The only medication proven to be beneficial in DMD is corticosteroids. Several studies have shown that prednisone at 0.75 mg/kg/day appears to increase muscle strength within 10 days, with its effects being maintained for at least 18 months. Because of its impressive results, patients who are older than 5 years and are ambulatory may receive steroids, with close monitoring for side effects. Another drug, deflazacort, which is a derivative of prednisolone, has also been studied because of having fewer side effects than prednisone; however this drug is not available in the United States (2). Because it is a genetic disease, genetic counseling is an important part of DMD management. Prenatal diagnosis is also possible for male fetuses using molecular genetic techniques like PCR through amniocentesis or chorionic villus sampling (8).

The prognosis for Duchenne muscular dystrophy is not good. Affected males with this progressive muscular disease become wheelchair bound before 13 years of age, are ventilator dependent in their late teens to early 20s due to respiratory failure, with death in their late 20s to 30s due to cardiac or pulmonary problems. Patients with Becker muscular dystrophy fare much better. Many remain ambulatory after age 16 years and survive through late adulthood (2). Despite the depressing nature of the muscular dystrophies, we are entering into a new age of molecular genetics, and perhaps in the near future we will have a cure for this crippling disease through gene therapy.

Questions

1. How are Duchenne and Becker muscular dystrophy inherited?
2. What protein is absent in Duchenne muscular dystrophy?
3. What is the Gowers' maneuver (or sign)?
4. What are some early signs and symptoms of Duchenne muscular dystrophy?
5. What is the average life expectancy for Duchenne muscular dystrophy? What do they die from? When do they lose ambulation?
6. By what age do almost all patients with Duchenne muscular dystrophy present with weakness?
7. Name three other organ systems, besides the musculoskeletal system, that are affected in Duchenne muscular dystrophy.
8. What is the only medication proven to improve weakness in DMD?

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Answers to questions
1. Both Duchenne and Becker muscular dystrophy are X-linked recessive.
2. Dystrophin.
3. The Gowers' maneuver is seen when a child climbs up on his thighs with his hands when going from a sitting to standing position. This is due to weakness in the knee and hip extensors.
4. Delay in walking, waddling gait, walking unsteadily with frequent falling, walking on toes, and difficulty at climbing stairs, Gowers' maneuver, and pseudohypertrophy of the calves.
5. 20 to 30 years. They die from pulmonary or cardiac problems. They lose ambulation before 13 years old.
6. 5 years.
7. Pulmonary, cardiac, and neurological (CNS).
8. Corticosteroids.

Chapter XVIII.15. Myopathy and Myositis
Dominic C. Chow, MD, MPH

A 6 year old girl presents to your office complaining of progressive weakness for the past two days. Her mother was alarmed this morning when her daughter had difficulty getting out of bed. Yesterday, she slept through most of the day and had a decreased appetite. She developed a low-grade temperature over night. For the past week, she has had a facial rash, which initially began as a reddish raised rash over both cheeks that has expanded to include the bridge of the nose. Coincidentally, her mother has also noticed a dry rash which developed over her daughter's elbows and knees, which she attributed to eczema. The child's medical history is unremarkable and she has been growing and developing appropriately. She is not on any prescribed or over-the-counter medications. Family history is negative for any connective tissue diseases or congenital disorders.

Exam: VS T 37.8, P 120, RR 18, BP 100/50. Wt 20 kg (50%tile), Ht 115 cm (50%tile). She appears subdued and weak. An erythematous plaque encompasses the cheeks and bridge of nose with diffuse borders, resembling a butterfly pattern. You notice a purplish-reddish hue over the upper eyelids along with some periorbital edema. There are several erythematous, scaly, and atrophic papules over her elbows and knees. A similar rash is seen over her interphalangeal joints of the hands. Examination of the nails reveals nailfold telangiectasias and erythema at the cuticles. She has trouble getting to the sitting position, and extreme difficulty getting to the standing position. No hypertrophy or atrophy of any muscle is noticed. Your examination confirms that she has profound symmetrical proximal muscle weakness. Cranial nerve testing and deep tendon reflexes are normal. Muscle fasciculations and infantile reflexes are absent.

Laboratory results: Antinuclear antibodies of (ANA) 1:640 speckled (normal range <1:160), sedimentation rate (ESR) 60 mm/hr (normal range 4-20), creatine kinase (CK) 490 IU/L (normal range 10-55), aspartate aminotransferase (AST) 500 IU/L (normal range 0-35), alanine aminotransferases (ALT) 250 IU/L (normal range 1-30).

Her initial symptoms are nonspecific except for the malar rash and eczema-like lesions on the flexor surfaces. Although this clinical picture is similar to systemic lupus erythematosus (SLE), the cutaneous findings along with the profound proximal muscle weakness make juvenile dermatomyositis (JDM) the more likely diagnosis. Treatment with prednisone (2mg/kg/d) is initiated and within days, she has resolution of her weakness. Her dermatologic symptoms gradually improve and the prednisone is gradually tapered over the course of several weeks.

The approach to the classification of neuromuscular disorders has aimed at distinguishing primary disorders of the muscle (myopathies and myositis) from disorders affecting peripheral nerves (peripheral neuropathies) (1). The spectrum of myopathies ranges from predominantly muscle disorders such as the muscular dystrophies, congenital myopathies, and myositis to multisystem disorders with muscle tissue involvement such as metabolic myopathies and myotonic dystrophy. Fortunately, the incidence of myopathies and myositis is rare. Myositis, which is the inflammation of muscle tissue, makes up the majority of these cases, with JDM as the dominant clinical entity.

In 1903 Steiner defined JDM as an acute, subacute or chronic disease of unknown origin, characterized by a gradual onset with vague and indefinite prodromata followed by edema, dermatitis, and multiple muscle inflammation (1). It is now classified as a rheumatologic condition whereby vasculitis is the etiology of the pathologic condition. JDM occurs in 3-4 cases per 1,000,000 with a predilection for females (2:1) and Caucasians (2). The peak age is 6 years, although there is a bimodal distribution of 5-9 and 10-14 years of age (2). Increased cases of JDM have been reported during the months of February through April (3). Familial cases of JDM are rare but there may be an immunogenetic predisposition among individuals who have the human leukocyte antigens HLA B8 and DR3 (4). The incidence of familial autoimmune diseases is not increased in cases of JDM. Although more common in adult dermatomyositis, JDM is not associated with underlying malignancy (5,6).

Myopathy and myositis commonly present as muscle weakness. The proximal muscles are usually involved although generalized weakness can be seen, especially in infants. Delayed motor milestones can be attributed to myopathic conditions, whereas delayed language and social adaptive behavior, and sensory impairment suggest a cerebral or neuropathic etiology. Myositis is often associated

with muscle tenderness over the affected muscles. The clinical presentation of JDM is insidious, often initiating as only fever and malaise. The clinical hallmarks of JDM are the characteristic dermatologic manifestations and profound weakness of the proximal muscles. An erythematous malar rash is commonly found, along with periorbital edema and violaceous discoloration of the upper eyelids (referred to as a heliotrope rash). Pathognomonic of JDM is the finding of Gottron papules, which are erythematous, scaly, atrophic plaques that occur symmetrically over the extensor surfaces of large and small joints. As seen with other vasculopathies, erythema at the cuticles and nailfold telangiectasias may be noted. Palpable and radiographically visible subcutaneous calcinosis is a common finding, occurring in 30-70% of cases (3). The muscle weakness is symmetrical and typically begins at the thighs, and later becomes generalized. A typical presentation entails difficulty in walking up stairs, difficulty in getting up from a chair or bed, and difficulty in combing one's hair. The Gowers sign (where the patient has difficulty rising to a standing position, using his/her hands to "climb up the legs") may be present. In the younger age group, generalized weakness often presents as the initial symptom. Prolonged muscle weakness may eventually lead to muscle contractures. Weakness of the oral muscles can result in nasal speech and dysphagia. Oral ulcers and abdominal pain stemming from vasculitis of the GI tract have been reported. Sun exposure may exacerbate JDM episodes.

Myopathic conditions such as JDM should be considered when evaluating patients with progressive muscle weakness. A methodical assessment of the patient's history and clinical examination is essential in determining the level of the lesion. Hypotonia can be broadly subdivided into myopathies (in which the pathology is confined to the muscle itself, with no associated abnormality in peripheral nerve) and neuropathies (in which muscle weakness is secondary to an abnormality along the peripheral nerve, such as the anterior horn cell to the neuromuscular junction). Myopathies typically present with muscle weakness that is accompanied with proximal atrophy with and without distal pseudohypertrophy, absent muscle fasciculations and infantile reflexes, normal to decreased deep tendon reflexes, and normal sensation (7).

Other hypotonic conditions can be distinguished from myopathies, using several clinical and electromyographic (with nerve condition studies) criteria. Deep tendon reflexes are usually hyperreflexic in upper motor neuron conditions (brain and spinal cord dysfunction), while they are hyporeflexic in anterior horn cell, peripheral nerve, neuromuscular junction and myopathy conditions. A Babinski sign and other primitive reflexes are likely to be present in upper motor neuron (brain and spinal cord) conditions, but they would likely be absent in most other conditions. Muscle fasciculations are likely to be seen in upper motor neuron and anterior horn cell conditions, but not likely to be seen in muscle or neuromuscular junction conditions. Electromyography (EMG) and nerve conduction studies can usually distinguish myopathic conditions from neuropathic conditions.

Inflammatory myopathies (myositis), which includes JDM, polymyositis, inflammatory myopathy associated with other connective tissue diseases, and acute viral myositis, can present with mild to severe muscle weakness. These disorders often have a bacterial, parasitic or viral origin, and have been linked with connective tissue diseases. The common feature of inflammatory myopathies is the involvement of the muscle through an inflammatory process. The above case is a classic presentation of JDM, where the dermatologic and progressive proximal muscle weakness are characteristic of the disease. Exact criteria for the diagnosis of JDM is as follow:

1) Characteristic rash.
2) Progressive symmetrical proximal muscle weakness.
3) Elevated muscle derived enzymes.
4) EMG changes - myopathic pattern.
5) Muscle histopathology - inflammatory changes.

Consistent clinical and laboratory findings are often enough to initiate therapy, sparing the patient from the invasive EMG and muscle biopsy procedures. EMG and muscle biopsy are beneficial when clinical and laboratory findings are inconsistent, or if initial therapy fails to resolve symptoms. Increased antibody titers and viral isolation of Coxsackie virus has led many investigators to consider it to be the causative agent for JDM (3).

The clinical presentation of polymyositis is identical to JDM except for the lack of the dermatologic manifestations. Polymyositis is predominantly a disease of adults, and is thought to have a rheumatologic etiology. In contrast to JDM, polymyositis has less primary vessel involvement seen on muscle biopsy and soft tissue calcifications are rare (3). Viral myositis can also present with proximal muscle weakness, but differs from other inflammatory myopathies by its propensity to affect calf muscles. Severe pain over affected muscle is typical and more pronounced than in JDM. Viral myositis usually occurs 1-2 days after an upper respiratory infection and is commonly attributed to influenza A and B infections (8). Rapid resolution occurs within weeks. Inflammatory myopathy in SLE is rare, especially in children. In rare cases of SLE induced myopathy, there is elevated double stranded DNA, reduced serum levels of complement, and presence of immune complexes much higher than that seen in JDM (3).

Hereditary myopathic disorders, such as muscular dystrophy and metabolic myopathies, can present as proximal muscle weakness. They typically manifest at birth but can present later in life. As discussed in the muscular dystrophy chapter, the neurologic findings of muscular dystrophies are consistent with a myopathic pattern, presenting as hypotonia in infancy or progressive weakness of proximal to distal muscles in childhood. Muscular dystrophies, however, lack the dermatologic changes seen in JDM and are gradual and progressive in nature. Some hereditary metabolic myopathies are not detected until late in childhood. Metabolic myopathies are rare and frequently fatal. They result from specific metabolic defects of glycogen, lipid, or energy metabolism, often due to mitochondrial dysfunction. These diseases, such as glycogenoses disorders, carnitine deficiencies, Kearns-Sayre syndrome, and myoclonic epilepsy and ragged red fibers (MERRF), often involve multi-organ systems such as the skeletal muscular, hepatic and nervous systems. Patients with hereditary metabolic myopathies report exercise intolerance, and muscle weakness/pain after exercise or stress. Dermatologic findings are absent.

Endocrinopathies can induce myopathic conditions, although the clinical symptoms associated with endocrine induced myopathies are typically that of muscle cramps and contractures. Derangements in thyroid and adrenal functions are the common endocrinopathies associated with myopathy. Thyrotoxicosis causes proximal weakness and wasting through the binding of thyroxine to myofibrils, which impair contractility. Hyperthyroidism may also induce myasthenia gravis and hypokalemic periodic paralysis (9). Likewise, hypothyroidism can cause muscle weakness, diffuse muscle hypertrophy ('myoedema') and inflammation (10). The correction of thyroid function results in the resolution of the myopathic condition. Corticosteroid induced myopathy (Cushing disease and Cushing syndrome) is associated with a nonspecific proximal myopathy with selective type 2 fiber atrophy (3). Adrenal failure produces nonspecific muscle weakness and in chronic cases, muscle contractures. Myopathy associated with diabetes and hyperparathyroidism have been described but are rare.

Hypokalemic periodic paralysis is an inherited autosomal disorder with full penetrance. The etiology of this paralysis is thought to be an abnormality of the muscle cell membrane, particularly an impairment of the calcium ion channel. Attacks of profound generalized weakness begin suddenly during the first and second decade of life. These episodes usually last for several hours and are triggered by

vigorous exercise, heavy carbohydrate meals, or anxiety. These patients present with profound hypokalemia (often less than 2.0). Potassium replacement usually results in fairly rapid recovery. Compared to JDM, patients with hypokalemic periodic paralysis are usually asymptomatic prior to and after these attacks.

Non-myopathic conditions should also be considered in patients with proximal muscle weakness. Guillain-Barre Syndrome (GBS) is an inflammatory polyradiculopathy, whereby the nerve roots and peripheral nerves are involved. Weakness follows an ascending pattern, progressing for several days to weeks, reaching a plateau, and then recovers over a period of several months. Reflexes are diminished, and patients can experience sensory abnormalities and severe back pain. There are no dermatologic findings in GBS. Lesions of the neuromuscular junction, such as myasthenia gravis, Lambert-Eaton myasthenic syndrome and botulism, can result in proximal muscle weakness. The weakness, often presenting as ptosis and diplopia, worsens with use and recovers with rest. In JDM, extraocular and facial muscles are rarely involved. Abnormalities of the peripheral nerve and neuromuscular junction do not have elevations in muscle derived enzymes and EMG findings are characteristic of the level of the lesion. Metabolic abnormalities such as hypophosphatemia and hypokalemia can result in muscle weakness but these symptoms are generalized.

Muscle derived enzymes (CK, myoglobin, AST, aldolase and lactic dehydrogenase) are elevated in JDM, representing damage to the muscle either through reduction in vascular supply or by direct immunogenic cytotoxicity. The CK elevation in JDM is usually in the range of several hundred, versus the much higher elevations in muscular dystrophies. Inflammatory markers such as ESR, white blood cell count, and ANA are commonly elevated. Von Willebrand factor-related antigen, a sensitive indicator of endothelial cell damage, has recently been used as a marker for JDM therapy (3).

EMG is a valuable tool in differentiating between myopathies and neuropathies, but is limited in further delineating the diagnosis. An EMG is performed by inserting a fine needle electrode into affected muscle to record its contractions. The procedure is painful and should be avoided in areas where future muscle biopsy may be planned. The typical EMG pattern in myopathies is that of low amplitude, polyphasic, potentials of short duration. Nerve conduction velocity is normal and unchanged with repetitive stimulation. These myopathic features suggest a myopathy as opposed to neuropathic findings which suggest a neuropathy.

A muscle biopsy can be beneficial in establishing the definitive diagnosis, especially in hereditary or congenital myopathies. Muscle biopsy is limited in that it is invasive and painful. It may not provide a specific diagnosis, if the muscle biopsied is not significantly affected by the disease process or if it not obtained appropriately. The quadriceps or biceps are typically biopsied in accessing proximal muscle weakness. The muscle histopathology of JDM shows infiltration with inflammatory cells, perifascicular atrophy, and capillary necrosis. Besides the usual histologic examination of the muscle tissue, specific staining procedures should be employed in differentiating JDM from hereditary disorders. Biochemical analyses on dystrophin protein levels assist in evaluating muscular dystrophies. Hereditary metabolic disorders should be evaluated with assays for glycolytic enzyme activity, respiratory chain enzyme complexes (i.e., oxidative phosphorylation enzymes largely found in mitochondria), carnitine levels, and fatty acid chain transport substrates. Electron microscopy can assist in evaluating mitochondrial abnormalities.

The treatment of JDM consists of immunosuppression and supportive care. Prompt initiation of corticosteroids reduces the long term complications of calcinosis and muscle contractures. Initial therapy can control muscle inflammation and gastrointestinal bleeding that results from vasculitis of the GI tract. Not uncommonly, the elevated muscle derived enzymes will normalize after the initial doses of corticosteroids. A maintenance dose of corticosteroids is titrated to normalize creatinine kinase levels and this is continued for approximately 1-2 years when re-occurrences, though rare, may develop (1,6). Other immunosuppressive agents, such as methotrexate, cyclosporin, and azathioprine are employed if corticosteroids are unable to reduce the inflammatory process. Nasogastric tube feedings may be necessary to protect the airways and in cases of severe dysphagia. Malabsorption of nutrients and medications can occur in cases of severe GI vasculitis, thus requiring parenteral nutrition and medication. Physical and occupational therapy programs are employed to avoid excessive deconditioning and to reduce muscle contractures.

Questions

1. True/False: Can sun exposure result in flare-ups in JDM?

2. What is the rate of recurrence in JDM?

3. Myopathies are most likely to cause:
   a. Delayed language skills.
   b. Sensory impairment.
   c. Delayed developmental motor milestones.
   d. Delayed social adaptive behavior.

4. Each of the following is true about myopathies, except:
   a. Distal weakness suggests a myopathic condition.
   b. Weakness is the primary symptom.
   c. Weakness or pain following exercise is a common feature of metabolic myopathies.
   d. Pain is not usually a feature of muscular dystrophies.

5. Which of the following (may be more than one) are typical of acute viral myositis but not JDM?
   a. Acute onset.
   b. Pain.
   c. Biceps involvement.
   d. Elevated CPK.
   e. Elevated ESR.
   f. Spontaneous resolution.

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Answers to questions

1. True. Sun exposure can exacerbate JDM dermatologic lesions and myositis, even during therapy. It is important to advise patients with JDM about appropriate sun protection - large rimmed hat, clothing over majority of body in sun, sunblock with a SPF of 15 or higher.
2. Unknown, but thought to be low. The risk of recurrence of JDM is highest in the first year after diagnosis, therefore maintenance prednisone is usually continued for 2 years.
3. c.
4. a
5. a, b and f are correct. Pain is typically greater in viral myositis than in JDM. Acute viral myositis has a propensity to affect the calf region, rather than the biceps. Both viral myositis and JDM have elevated CPK and ESR so these tests do not distinguish the two.

Chapter XVIII.16. Developmental Brain Anomalies

Kaipo T. Pau

This is an 5 month boy who is brought to the emergency room after his mother noted that he had a seizure. His mother adds that she is also concerned because her son has always seemed weak for his age and that his head seems to be progressively swelling, increasing out of proportion to the rest of his body. In addition, his strength and degree of development does not seem to follow that of his older brother. There is no recent history of fever, vomiting, diarrhea, poor appetite or urinary abnormalities.

He is the second child born to 31 year old parents. There is no family history of recurrent abortions, consanguinity, or mental retardation. Pregnancy was uncomplicated and he was born with a weight of 2500 g, a length of 47 cm, a head circumference of 32 cm, and Apgar scores of 8 and 9.

Exam: VS T 37.2, P 100, RR 38, BP 75/55. Height 64 cm (25%ile), weight 6.8 kg (25%ile), and head circumference 45 cm (98%ile). He is subdued in no distress. He is not irritable, but he does not move about much. Diffuse hypotonia is obvious upon visual inspection and the child is lethargic and inactive. His head is macrocephalic. His anterior fontanelle is open and rather large for age. Abnormal facies showing a short nose with nostrils displaced forward is noted. Deep tendon reflexes are very brisk (3+) and there is a positive Babinski sign bilaterally. His eyes are opened wide and a downbeat nystagmus is present.

A CBC and chemistry panel are normal. A CT scan of the brain shows a smooth appearance of the cerebral cortex, with shallow sulci and thick gyri (pachygyria). The ventricles are dilated (hydrocephalus) and a Chiari malformation obstructing CSF outflow is noted. After his mother agrees, he is taken to the operating room for insertion of a ventriculoperitoneal shunt.

Although the incidence of nervous system malformations in living newborns is 1%-3%, such malformations are present in 40% of infant deaths. The etiologies associated with developmental anomalies may result from a variety of insults from genetic to environmental. Abnormalities associated with the neural tube and the neural plate generally occur within the first 28 days of gestation. On the other hand, abnormalities associated with cellular proliferation and migration in the CNS generally occur after the 28th day of gestation. This chapter will cover malformations associated with both of these periods. Included among these malformations are Arnold-Chiari malformations and a group of disorders collectively referred to as neuronal migration defects (1).

Professor Hans Chiari, a German pathologist described a group of malformations characterized by the displacement of the cerebellum. He classified the manifestations into types based on the order of increasing severity (type I being least severe) and these became known as Chiari malformations (2). Of note, type II Chiari malformations (CM) are also known as the Arnold-Chiari malformation. However, other publications use "Arnold Chiari" malformations as the umbrella term for the four types of cerebellar displacement. This chapter will look at the Chiari malformations that are more commonly seen (1,3).

Type I CM is defined as a caudal displacement of the cerebellar tonsils below the foramen magnum by 5 mm. Hydrocephalus is present in 90% of patients and syringomyelia may also be present. Patients may live asymptomatically up until the third or fourth decade of life or later, when signs and symptoms of this disorder may present. The presentation is dependent upon the degree of the abnormality and associated manifestations, on neural structures. These can include lower cranial neuropathies, downbeat nystagmus, ataxia, vertigo, vocal cord paralysis, and eye movement abnormalities (3). Additional skeletal anomalies include scoliosis (especially from syringomyelia) and skull base abnormalities (2). The differential diagnosis of type I can vary tremendously, depending on the neural structures involved. A diagnosis of type I can be made on the basis of imaging (MRI is preferred) along with clinical information. Treatment is done surgically by cervical bony decompression of structures in the foramen magnum and along the spinal cord if necessary. This process involves removal of bone (usually by cutting through bones of the spine). Relief of signs and symptoms related to the compression of the brain

stem is better than those related to the spinal cord (2). Treatment of hydrocephalus involves finding an alternative route of drainage of the cerebrospinal fluid in the ventricles. This is usually accomplished by a ventriculoperitoneal shunt (4). Successful interventions may allow the individual to have normal mental development, if there are no additional CNS malformations (2).

Type II (Arnold-Chiari) malformation is the commonest type of CM malformation (4). It is manifested by an increased caudal displacement of the cerebellum into the foramen magnum, along with the lower brainstem. Myelomeningocele is usually associated with this type II malformation usually resulting in hydrocephalus (80% or more). There is an increased likelihood to develop hydrocephalus if the meningomyelocele is more rostral. As in type I, the presentation of signs and symptoms depends upon the degree of the abnormality and associated manifestations, on neural structures. Symptoms related to hindbrain dysfunction may develop which include difficulty feeding, choking, stridor, apnea, vocal cord paralysis, pooling of secretion, and spasticity of the upper extremities. An increased head circumference may be present due to hydrocephalus. Ventricular enlargement may be slow or rapid and cause a bulging anterior fontanel, dilation of scalp veins, irritability, and vomiting. Diagnosis is the same as type I but a more severe displacement is seen, and a myelomeningocele is usually obvious on gross inspection. Treatment is done surgically to repair the myelomeningocele and to relieve the hydrocephalus. Bony decompression may also be performed. Prognosis depends on the site and severity of myelomeningocele. Improved prognosis is associated with a more caudal lesion. It is also advisable to recommend a multivitamin with folate for expectant mothers to reduce the risk of subsequent neural tube defects (3).

Type III (rare) CM is characterized by a cerebellar displacement into an occipital encephalocele. An occipital encephalocele is a defect in the closure of the neural tube near the base of the skull, a condition known as occipital encephalocele. Prognosis is poor (4).

Neuronal migration defects form a group of developmental brain anomalies. Abnormal cerebral cortical development is generally viewed as an improper migration of neural tissue. In other words, neurons fail to reach their destination in the cortex in the period of cortical neurogenesis beginning around 10 to 12 weeks of gestational age or earlier. Environmental factors such as retinoic acid, radiation, and methylmercury have been implicated in the pathogenesis. Viral infections in utero are also known to result in migrational abnormalities, although the mechanism of action is unknown. The abnormalities, which may present together, can be grouped into three general categories. They include lissencephaly/pachygyria, polymicrogyria, and heterotopia.

It is thought that lissencephaly and pachygyria are different representations of the same manifestation. Lissencephaly (means smooth brain) refers to a more diffuse bilateral brain abnormality and pachygyria (thick gyri) is a more focal or multifocal abnormality. The basic abnormality, seen on imaging and on gross pathologic examination, is the smooth surface of the cerebral cortex. The cortex is also noticeably thickened with a relative abundance of gray matter, compared to white matter which is variably preserved. There are at least 2 types of lissencephaly (2).

Autosomal and X-linked forms of type I lissencephaly have been identified, but this type may also be associated with other syndromes such as the Miller-Dieker Syndrome (about 15% of cases) (5). A cross-section of the brain reveals an extremely thick cortex organized into four abnormal layers, rather than the usual six. In type I lissencephaly, seizures and severe mental/psychomotor retardation are present. Most cases of type I present in the neonatal period with marked hypotonia, and later with weakness in all four extremities. In the Miller-Dieker syndrome, characteristic facial features are present in childhood and include a prominent forehead, bitemporal hollowing, a short nose with anteverted nostrils, a prominent upper lip, and jaw abnormalities. Lissencephaly as an isolated abnormality is distinguished from the Miller-Dieker Syndrome based on these facial characteristics. Diagnosis of lissencephaly is based on the smooth surface finding along with a widely opened Sylvian fissure on neuroimaging. Cytogenetic studies may often reveal a deletion on the LIS-1 (lissencephaly gene) in chromosomal region 17p13.3. Treatment of the disorder involves seizure medications and supportive care. The prognosis for type I lissencephaly, when associated with other entities, is generally poor and many patients do not survive into childhood.

The inheritance for type II is autosomal recessive but there has not been any association with a specific gene or locus. In contrast to type I, type II lissencephaly is often associated with congenital muscular dystrophies that often involves the eyes as well. Examples are the Walker-Warburg syndrome and the Finnish muscle-eye-brain disorder. In type II lissencephaly the surface of the cerebral cortex usually presents as a diffuse smooth brain appearance. A cross-section reveals an increased thickening of grey matter. Clinical manifestations, when seen with associated muscular dystrophies will involve abnormalities of muscle and CNS development. This may include neonatal hypotonia and eye abnormalities (e.g., retinal dysplasia, cataracts, microphthalmia), and joint contractures. Laboratory results reveal elevated creatine kinase levels (from the muscular dystrophy). Diagnosis is made by careful examination of the MRI of the cortex. Treatment and prognosis of type II is basically the same as in type I.

Polymicrogyria (also known as microgyria, meaning small gyri) is also considered to be a migrational disorder (defects seem to occur between week 17 to 18 and weeks 24 to 26 gestation). Unlike lissencephaly and pachygyria, the border between the polymicrogyria and normal cortex is distinct. Polymicrogyria usually reveals a cerebral cortex with a complex set of small gyri appearing fused together. This gives the surface of the cortex a fine stubbling appearance. A number of malformations and abnormalities have polymicrogyria as one part of an overlying CNS manifestation. For instance the polymicrogyria-schizencephaly complex is a disorder with clinical features including delayed development, pyramidal signs, motor speech dysfunction and epilepsy. Schizencephaly (means cleft brain) is the presence of fused or unfused, unilateral or bilateral clefts within the cerebral hemispheres as a result of abnormal morphogenesis (3). Polymicrogyria presents with psychomotor retardation and frequent focal seizures. The differential diagnosis for this disorder can include Aicardi's, Neu-Laxova, Zellweger, and Smith-Lemli-Opitz syndromes. Removal of a focal area of polymicrogyria may be curative. Multifocal removal may result in improved seizure control. The prognosis is variable, but usually poor.

Cerebral heterotopia are defined as focal or multifocal disorganized nodules of gray matter at inappropriate places in the cerebrum. The heterotopia may be found incidentally on imaging or there may be associated clinical manifestations that present itself. The main presenting feature is a childhood seizure disorder of various types including focal, multifocal, and generalized. Motor and mental retardation may also be present depending upon the extent of the heterotopia abnormality. Focal area heterotopia removal may improve seizures (2).

Questions

1. What is the most common type of Chiari malformation?

2. What CNS structure is displaced in Chiari malformations?

3. What are the 3 general categories of neuronal migration abnormalities?

4. What basic abnormality is revealed with lissencephaly on MRI imaging and gross inspection?

5. What other abnormalities are often found with type II Chiari malformations?

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Answers to questions

1. Type II (Arnold-Chiari malformation).
2. Cerebellum.
3. Lissencephaly/pachygyria, polymicrogyria, heterotopia.
4. Smooth surface of the cerebral cortex.
5. Myelomeningocele and hydrocephalus.

Chapter XVIII.17. Reye Syndrome
David W. Boldt

This is a 2 year old child who appears to be recovering from an upper respiratory infection when he develops vomiting. He may have taken aspirin (given by his grandmother), but he was supposed to have taken acetaminophen. He initially presents to the emergency department with irritability and restlessness. He subsequently develops convulsions which are treated with anticonvulsants and he is admitted to the ICU.

Exam: VS T 37.8, P 100, RR 50, BP 110/70, oxygen saturation 99% in room air. Height, weight, head circumference are at the 50th percentile. He is agitated and not cooperative. Head shows no signs of external trauma. Pupils are equal and reactive to light. Conjunctiva are clear, sclera non-icteric. EOMs cannot be fully tested, but they are conjugate. TMs are normal. Mouth is not easily examined. Neck reveals no adenopathy. He is agitated so it is not possible to be certain that his neck is supple. Heart regular without murmurs. Lungs are clear. Abdomen is flat with normal bowel sounds. It is difficult to tell if he has any hepatosplenomegaly. No definite tenderness. No inguinal hernias are present. Testes are normal. He moves all extremities. Reflexes are not testable because of his agitation.

Labs: Serum bilirubin: Normal. Serum AST and ALT: increased. Serum ammonia: increased. Prothrombin time: prolonged. A CT scan of the brain is obtained which shows cerebral edema.

His neurologic symptoms rapidly worsen and he becomes unresponsive. He is intubated and put on mechanical ventilation.

Reye syndrome is suspected. A confirmatory liver biopsy reveals diffuse, small lipid deposits in the hepatocytes (microvesicular steatosis) without significant necrosis or inflammation. These findings are consistent with the diagnosis of Reye syndrome.

Reye syndrome (also called Reye's syndrome) is a rare illness seen exclusively in children less than 15 years of age. It is characterized by fatty changes in the liver and encephalopathy that often leads to coma. The number of cases of Reye syndrome has decreased in the last decade due to increased awareness concerning the use of aspirin (salicylates) in children.

Common signs and symptoms include vomiting, agitation, irrational behavior, progressing to lethargy, progressive stupor, restlessness, and convulsions. The usual progression of Reye Syndrome follows the following course: A febrile illness, chickenpox, or upper respiratory infection, occurs in a previously healthy child, followed by a period in which the child seems to have recovered. Subsequently, vomiting ensues 5-7 days after the onset of the initial illness. Simultaneously or within a few hours of this onset of vomiting, delirium, restlessness, and stupor usually occur. In severe cases, the neurologic symptoms rapidly progress to seizures, coma, and eventually death.

Reye Syndrome can be broken down into five stages. This may be preceded by a stage of agitation sometimes called Stage 0. Stage I: Patient is quiet, lethargic, sleepy, and is vomiting. Lab values indicate liver dysfunction. Stage II: Characterized by deep lethargy, confusion, delirium, combative behavior, hyperventilation, and hyperreflexia. Stage III: The patient is obtunded. Seizures may be present at this stage. There is decorticate rigidity with intact pupillary light reflexes. Stage IV: Seizures are present and are accompanied by a deepening coma, decerebrate rigidity, loss of oculocephalic reflexes, and fixed pupils. Stage V: Characterized by coma, areflexia, respiratory arrest, fixed and dilated pupils, and intermittent flaccidity and decerebrate posturing. The EEG at this point is isoelectric.

There is almost always a history of a preceding viral illness, especially influenza A or B, or varicella. Examination may reveal a positive Babinski sign and hyperreflexia, consistent with cerebral edema; dilated, sluggish pupils, and hyperpnea with irregular respirations. Hepatomegaly is sometimes present, but splenomegaly is absent.

Lab findings include hyperammonemia, normal or slightly elevated bilirubin and alkaline phosphatase, prolonged prothrombin time, hypoglycemia (variable), and moderate to severe elevations in AST, ALT, and lactate dehydrogenase. Hyperaminoacidemia (glutamine, alanine, and lysine) and hypercitrullinemia can be found but these require special tests. Tissue histopathology demonstrates microvesicular steatosis of the liver, kidneys, and brain. The CSF analysis is normal, but the CSF pressure (i.e., ICP) is elevated.

Epidemics of Reye syndrome seem to occur during epidemics of influenza B virus. The use of salicylates (aspirin) is associated with Reye Syndrome, and therefore its use is contraindicated in children (acetaminophen or ibuprofen is usually recommended instead).

The proposed pathological mechanism in Reye is mitochondrial damage caused by salicylate metabolites or some other toxin during a viral infection. Mitochondrial damage leads to elevated short chain fatty acids, hyperammonemia, and directly to cerebral edema. In very young children, metabolic defects in fatty acid oxidation may contribute to the pathogenesis.

The diagnosis of Reye syndrome is based largely on clinical findings, after ruling out other causes of neurologic deterioration such as other encephalopathies, encephalitis, toxins, neoplasms, hepatic failure, fulminant hepatitis, fatty acid oxidation defects, other metabolic disorders, hemorrhage, etc. Histopathology and electron microscopy of a liver biopsy can be used to confirm the diagnosis, but this is usually not done clinically. Urine gas chromatographic analysis and serum acyl-carnitine levels will help to differentiate Reye Syndrome from metabolic disorders. Systemic carnitine deficiency (SCD) (which is an inherited defect of fatty acid oxidation), results in hypoglycemia, hyperammonemia, hypoprothrombinemia, and acute episodes of encephalopathy. SCD mimics the clinical picture seen in Reye Syndrome. In these patients, acyl-carnitine levels would be elevated, whereas they would be normal in patients with Reye syndrome.

Brain imaging studies (CT, MRI) are useful to rule out other causes of CNS dysfunction. Patients with Reye syndrome will generally exhibit findings of cerebral edema and increased intracranial pressure.

Treatment for Reye syndrome is supportive. Hypoglycemia is corrected if present. Measures to lower intracranial pressure (ICP) are initiated. Intensive care measures to monitor fluid status and physiologic function should be initiated (NG tube, Foley catheter, oximetry, ECG, arterial and central venous pressure lines). If the patient is in grade 3 coma (see below), mechanical ventilation may be necessary.

Coma can be scored using the Glasgow coma scale. A simpler method is the AVPU scale (A=alert, V=responds to verbal stimuli, P=responds to painful stimuli, U=unresponsive). Similarly, grades can be used as follows: Grade 1=Subject is able to obey simple commands. Grade 2=No response to commands, but purposeful responses to pain are elicited. Grade 3=Non-purposeful responses to pain (e.g., sternal rub). Grade 4=No response to painful stimuli. Grade 5=Autonomic dysfunction with hypothermia, cardiovascular instability and absent spontaneous respiration.

Intracranial pressure should be monitored directly which is best done with a ventricular catheter and kept below 15-20 mmHg through the use of periodic mannitol infusions (0.5-1g/kg every 4 hours), barbiturates, or ventricular CSF drainage. Systemic blood pressure should be monitored and kept high enough to maintain cerebral perfusion pressure (the difference between mean arterial pressure and intracranial pressure) above 45-50 mmHg.

Maintenance fluids using 10% glucose (to reverse hypoglycemia and to some degree as an osmotic agent) should be given at a rate sufficient to produce a urine flow of 1.0-1.5 ml/kg/h. Vitamin K, 3-5 mg intramuscularly, should be given to reduce the likelihood of coagulopathy due to vitamin K dependent factor depletion. Induced hypothermia (30-33 degrees C) and pentobarbital (10-50/mg/kg/day) can be used to decrease the brain's metabolic needs during periods of elevated intracranial pressure.

Reye syndrome is a serious neurologic condition, but roughly 70% of patients with Reye syndrome survive. Survival is related to the depth of the coma and the peak ammonia level on admission. Complications due to coma such as aspiration pneumonitis and respiratory failure also affect the prognosis. If death results, it is usually from refractory cerebral edema. Severe neurologic dysfunction may be present in children who recover from prolonged grade 3 or 4 coma. All patients should be screened for fatty acid oxidation defects and other metabolic defects.

Questions

1. True/False: Reye syndrome is most often preceded by a history of viral illness.

2. The cause of Reye syndrome is:
   a. liver failure
   b. brain abscess
   c. unknown
   d. too much fat in the diet

3. Which drug is associated with the development of Reye syndrome?
   a. antidepressants
   b. salicylates
   c. cancer chemotherapy
   d. barbiturates

4. Reye syndrome is primarily a disease of:
   a. adults
   b. the elderly
   c. children and adolescents
   d. infants

5. What is/are the most common feature(s) of Reye syndrome?
   a. liver infection
   b. rapid accumulation of fat in the liver
   c. inflammation of the brain
   d. b and c

6. Treatment of Reye syndrome focuses on:
   a. Maintaining cerebral perfusion.
   b. Ammonia removal or detoxification.
   c. Treating hypoglycemia.
   d. Preventing urinary tract infection.

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Answers to questions
1.True, 2.c, 3.b, 4.c, 5.d, 6.a

Chapter XVIII.18. Brain Tumors
Wade T. Kyono, MD

A 10 year old female with intermittent headaches for 3-4 months, complains of blurry vision. She is referred to a pediatric ophthalmologist for her blurry vision, when she is noted to have medial deviation (adduction) of her left eye. An MRI scan is done and this shows a pituitary mass. She is referred to a pediatric neurosurgeon who performs a gross total resection of the primary tumor. The tumor pathology is consistent with the diagnosis of craniopharyngioma. A follow-up MRI scan done within 48 hours of her tumor resection demonstrates no residual tumor. While she continues to have no recurrent tumor 2 years after her resection, she has persistent clinical problems related to the craniopharyngioma and its resection. Vision in her left eye is severely impaired. Cognition, concentration and memory appear to be adversely affected with decreased school performance. Growth has decreased and she requires growth hormone and thyroid hormone replacement. Neuropsychiatric testing is performed by a clinical psychologist. An individualized education plan is developed and she receives support services/tutoring.

Central nervous system (CNS) tumors have the dubious distinction of being the most common solid tumor of childhood. They represent the second most common malignancy in children (17%). There are approximately 2500 new brain tumor cases per year nationally. Infratentorial cerebellar and brain stem tumors are more common in children than adults. In contrast, cerebral tumors, mostly astrocytomas, are most common in adults. Of the pediatric brain tumors, 35-50% are astrocytomas, 10-20% medulloblastomas/primitive neuroectodermal tumors (PNET), 10-20% brain stem gliomas, 5-10% ependymomas, 5-10% craniopharyngiomas, 1-2% pineal tumors, and 10-15% other. Many of these tumors are undifferentiated and defy standard histologic classification. The incidence is higher in males versus females. There appears to be a small peak in embryonal tumors with a relative paucity of adult type gliomas until adolescence. One third of all brain tumors in children younger than 15 years of age occur in children under 5 years of age. The overall incidence of childhood brain tumors has been increasing over the past several decades, with some of this increase due to improved detection with computed tomography (CT) and magnetic resonance imaging (MRI) scans. Overall mortality and morbidity likely exceeds that of other common solid tumors and leukemia. Long term side effects of CNS tumors account for high rates of morbidity due to the location of primary lesions and aggressive therapy received by patients.

Factors that are associated with an increased risk of pediatric brain tumors include being male (medulloblastoma/PNET, ependymomas), ionizing radiation, and genetic conditions (neurofibromatosis, tuberous sclerosis, Turcot syndrome, and Li-Fraumeni syndrome). Cured meats and polyomaviruses (simian virus 40, JC, BK) have been also been implicated in the development of brain tumors. In general though, the majority of pediatric brain tumors arise with no obvious risk factors present.

Despite the progress made over the last 20-30 years in treating childhood cancer, pediatric brain tumors have demonstrated only modest improvements in survival. While from 1975-1995 the mortality rate for leukemia and all other non-central nervous system (CNS) cancers declined by over 50%, CNS cancers had only a 20% improvement in survival. The lack of improvement in brain tumor treatment is dependent on many factors which include: 1) the presence of the blood brain barrier, 2) the low regenerative capacity of the brain, and 3) the inability to intensify CNS toxic treatment without unacceptable long term developmental side-effects (pronounced in younger children). Despite the development and use of chemotherapy agents and radiation therapy over the last 20 years, the primary determinant of survival for the majority of pediatric brain tumors remains the degree of surgical excision. Improvements in the delivery of localized radiation therapy (conformal radiation), stereotactic radiation (gamma knife), dose-intensified treatment with bone marrow transplantation, and the development of new, targeted anti-tumor therapies hold promise for future improvement in treatment.

The most common presentations of brain tumors in children include flu-like symptoms; frequent headaches that are worse in the morning and associated with nausea and vomiting; seizure activity (more likely in slowly growing supratentorial tumors); unsteady gait; vision changes; and deterioration of school performance without explanation. Age of children also affects diagnosis, with younger children and infants suffering from more nonspecific symptoms. Infants with open fontanelles and cranial sutures that are not fused may be very nonspecific signs of tumor progression. The nonspecific nature of these symptoms are often misleading to the general practitioner so that care must be taken in evaluating children with persistent or worsening symptoms.

For older children infratentorial tumors generally present with problems of truncal steadiness, coordination, gait, or cranial nerve function. Nonlocalizing presenting signs suggestive of increased intracranial pressure are often found with tumors that fill the posterior fossa, while infiltrative tumors of the cerebellar hemispheres often present with an asymmetric inability to coordinate and direct limb movements. Seizures are most frequently found in slow growing supratentorial gliomas so that CT or MRI scans are indicated for all children with new onset focal and complex seizures, and most children with unexplained generalized seizures to rule out a brain tumor. Children with metastatic tumors (some primitive neuroectodermal or germ cell tumors) often present with metastases to the spinal cord and cauda equina, and may have back pain, urinary incontinence, or focal extremity weakness or sensory loss.

CNS symptoms associated with brain tumors can be used to determine brain tumor location. Brain stem tumors often result in motor and sensory changes, and the impairment of vital functions (cardiac, respiratory, vasomotor). Cerebellar lesions often present with abnormalities in balance, posture, or motor coordination (including eye movements). Frontal lobe tumors may affect attention, behavior, abstract thought, reflection, problem solving, creative thought, emotion, intellect, judgment, initiative, inhibition, coordinated movements,

generalized and mass movements, some eye movements, muscle movements, skilled movements, sense of smell, physical reaction, or sexual urges. Parietal tumors may affect the appreciation of form through touch (stereognosis), tactile sensation, response to internal stimuli (proprioception), sensory combination and comprehension, some language and reading functions, or some visual functions. Occipital lobe lesions may affect reading or vision. Pituitary gland lesions affect hormonal body processes, physical maturation, growth (height and form), sexual maturation, and/or sexual function. Spinal cord tumors result in sensory and motor defects. Temporal lobe defects may affect auditory memories, hearing, visual memories, visual pathways, memory, music, fear, language, speech, or behavior.

Common findings within more general classifications of brain tumors occur as follows:

INFRATENTORIAL (Brain stem and cerebellar).

Brain stem: 1) inability to deviate both eyes conjugately, 2) problems with adducting an eye on lateral gaze, 3) cranial nerve V, VII, and IX defects.

Cerebellopontine angle: facial weakness, hearing loss, unilateral cerebellar deficits.

Brain stem or posterior fossa: peripheral VII nerve palsy (upper and lower facial weakness).

Above pons: central VII nerve palsy (lower facial weakness).

Hypothalamic, brain stem, or upper cervical cord: partial Horner's syndrome (ipsilateral ptosis and miosis).

SUPRATENTORIAL.

Upper motor neuron signs: hemiparesis, hyperreflexia, clonus and sensory losses.

Frontal or parietal-occipital, third ventricle: may have no focal deficits (present with increased ICP).

Optic nerve or chiasmal defect: visual deficits, Marcus Gunn pupil (afferent pupillary defect), bitemporal hemianopsia (classic chiasmal tumor), unilateral or bilateral nystagmus with head tilt (chiasmal).

Hypothalamic: "diencephalic syndrome" (failure to thrive and emaciation in a happy and hungry child).

Pineal tumors: Parinaud's syndrome - poor upward gaze, slightly dilated pupils that don't react to light but react to accommodation, retraction or convergence nystagmus, lid retraction.

The initial diagnosis is largely based on imaging. A CT scan is often used in initial screening because of its relative speed or in cases where MRI is not available. MRI scan is the neuroimaging scan of choice. T2 weighted images enhance the differences between normal and tumor tissues. Gadolinium-DPTA, given as a contrast agent, further improves the sensitivity of MRI. MRA (magnetic resonance angiography) is useful if tumor vascularity is a concern.

Cerebrospinal fluid examination in conjunction with MRI will help to demonstrate spinal cord lesions caused by PNETs, anaplastic gliomas, and germinomas. PET scanning is useful in distinguishing between radionecrosis/scar tissue and recurrent or residual tumor. Neuropathologists experienced in pediatric brain tumor histopathology and cytology add considerably to the accuracy of pathologic diagnosis.

Specific tumor types tend to occur in specific areas of the brain, which can provide useful information in determining the tumor diagnostic type. Infratentorial tumors are likely to be brain stem gliomas, cerebellar astrocytomas, primitive neuroectodermal tumors (medulloblastomas), or ependymomas. Supratentorial tumors are likely to be choroid plexus tumors, otic/hypothalamic astrocytomas, or high grade gliomas. Pineal tumors are likely to be pineoblastoma, germ cell tumors, or astrocytoma. Craniopharyngiomas tend to occur in the suprasellar or intrasellar region. Gliomas in the visual pathway are likely to be a low grade pilocytic astrocytoma, or fibrillary astrocytoma. Intramedullary spinal cord tumors are likely to be astrocytomas, ependymomas, oligodendroglioma, gangliogliomas, or malignant gliomas. Disseminated brain tumors (15% of primary tumors) are likely to be medulloblastoma, germ cell tumors, ependymoma, or high grade gliomas.

Treatment options include neurosurgery, radiotherapy (radiation therapy) and/or chemotherapy. Acute complications of radiotherapy include: alopecia (temporary or permanent), erythema and desquamation of skin, otitis externa/media, hearing loss, and bone marrow suppression. Late complications include: radiation necrosis, headache, personality change, seizures, lethargy, hemiparesis, ataxia, increased ICP, focal neurologic signs, vasculitis with transient ischemic attacks and infarction, second malignancies (soft tissue sarcomas, meningiomas, others), somnolence syndrome (4-8 weeks after radiation therapy), necrotizing leukoencephalopathy (4-12 months after therapy), neuropsychologic damage (peaks 3 years after treatment), and endocrine dysfunction. Chemotherapy is limited by the blood brain barrier. In the majority of studies utilizing post-operative chemotherapy, overall survival is most directly related to the degree of primary resection. Efforts to delay radiotherapy by using chemotherapy first have generally resulted in poorer outcomes. High dose chemotherapy, often in conjunction with autologous bone marrow transplantation and reduced radiotherapy doses, in infants and younger children is being investigated. Future use of immunotherapy, gene transfer therapy, blood brain barrier disruption, and novel molecularly targeted therapy hold hope for future treatment efforts.

In general, prognosis is worsened by younger age (particularly infants), increased tumor size, metastatic disease, subtotal resection, unresectability, histologic aggressiveness, decreased radiotherapy, and molecular markers associated with poor outcomes. Side effects are probably most pronounced in children who are the youngest at diagnosis and treatment. IQ decreases, memory problems, fine motor, and visual disturbances may cause long term problems. Cognitive deficits, learning problems, and behavioral problems often occur.

Routine MRI surveillance should be performed every 3 to 6 months during the first 2 years, every 6 to 12 months for the next 2 to 3 years, and every 3 to 5 years thereafter to detect late events (meningiomas from radiation therapy). Medulloblastoma and other embryonal tumors should have spinal MRIs done for the first 2 years. Neuroendocrine problems include growth retardation from impaired growth hormone secretion, hypothyroidism, premature or delayed puberty, all of which may not be immediately obvious. Yearly endocrine and neuropsychologic testing is highly recommended for all CNS tumor patients. Evaluation and/or services for children with special health care needs should be initiated for all brain tumor patients to deal with long term sequelae.

Questions

1. Which statement(s) about pediatric brain tumors are true:
    a. Most common childhood solid tumor.
    b. Brainstem and cerebellar locations more common than adults.
    c. Incidence rate appears to be increasing.
    d. Overall survival has not kept pace with other childhood tumors.
    e. All of the above.
    f. b and d only.

2. Which of the following is not a common presenting sign of brain tumors?
    a. Visual problems
    b. Fever
    c. Seizure
    d. "flu-like" symptoms
    e. Headaches with early morning emesis

3. Brain stem tumors:
    a. Should always be biopsied
    b. Are infratentorial
    c. Can be cured with aggressive resection
    d. May present with cranial nerve abnormalities
    e. All of the above
    f. b and d only

4. Which of the following is most consistent with improved long-term survival in children with brain tumors?
    a. Young age at diagnosis
    b. Subtotal tumor resection
    c. Brain stem location
    d. Gross total tumor resection
    e. The use of regular-dose chemotherapy

5. Long term sequelae of brain tumors in children include:
    a. Decreased cognition
    b. Impaired memory
    c. Growth hormone deficiency
    d. Delayed puberty
    e. All of the above

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Answers to questions

1.e, 2.b, 3.f, 4.d, 5.e

Chapter XVIII.19. Arteriovenous Malformations
Chia Sonia Granda

This is a ten year old male who presents to the emergency department (ED) via ambulance, unconscious. His soccer coach accompanies him and reports that before practice began, he was complaining of a headache, and one hour later, he fell and began convulsing while practicing on the soccer field. A parent called 911. He seized for approximately five minutes. An ambulance arrived about 5 minutes later. An IV was started and he received phenytoin en route to the ED. His mother arrived shortly afterward, reporting that her son has a history of occasional headaches and that his teacher feels that he may have difficulty concentrating.

Exam: VS T 37.1, P 90, RR 24, BP 90/60, oxygen saturation 100% in room air. Height, weight, head circumference are at the 50th percentile. He is drowsy with a good respiratory effort. A contusion is noted on his left forehead. His pupils are equal and reactive. Auscultation reveals a bruit over the right eyeball. Ear and mouth examination is normal. Neck, heart, lung, and abdomen exams are normal. His muscle tone is diminished and his deep tendon reflexes are normal. He has a questionable Babinski sign bilaterally. His overall color and perfusion are good.

A CT scan demonstrates a large arteriovenous malformation (AVM) in the basal ganglia. He is admitted to the hospital. An MRI scan demonstrates that the AVM is most likely inoperable, and this is confirmed by angiography. The patient and his parents are warned of the possible risks associated with treatment of his AVM, and choose embolization as their treatment choice. Five years later, he dies due to a hemorrhagic stroke in his posterior cranial fossa.

An arteriovenous malformation (AVM) is defined as a tangled collection of abnormal blood vessels where there is an abnormal communication between the arterial and venous systems. They are not neoplastic despite their tendency to expand with time and the descriptive term "angioma" is occasionally applied. The afferents flow directly into the venous efferents without the usual resistance of an intervening capillary bed. They are mostly congenital. AVMs represent abnormal embryonic and fetal morphogenesis during the retiform stage of development of endothelial channels (approximately day 48 of human embryogenesis).

These lesions are neither neoplastic nor proliferative, rather growing commensurate with the child. If large enough, they may produce a shunt of sufficient magnitude to raise the cardiac output. In extreme circumstances, this can cause high output congestive heart failure. Common sites include skin, liver, brain, brainstem and spinal cord, where they may cause headaches, seizures or bleeding (subarachnoid hemorrhage). These lesions do not improve or resolve with time. In children, AVMs are the most common lesion associated with spontaneous hemorrhage. Only cerebral AVMs, of this broad classification, will be considered in this chapter.

Patients with small AVMs are more likely to present with hemorrhage than are those with large AVMs, partly because small AVMs are less likely to cause seizures and progressive neurologic deficit since a small cortical area is usually involved. About 40-60% of patients with an AVM present with hemorrhage, often with an intracerebral or intraventricular component. In comparison with saccular aneurysms, AVMs tend to bleed in younger patients, i.e. 20-40 years, and are less likely to have a fatal outcome. Lesions in the posterior fossa have a greater incidence of death from hemorrhage. The evidence is controversial as to whether patients who harbor an AVM that has bled are more likely to suffer further bleeds than those patients with other presentations.

Children present in a similar way to adults, but they may also present with high output cardiac failure if there is a high volume shunt, and they may rarely present with hydrocephalus. Approximately one third of patients present with seizures. Generalized or partial seizures commonly occur in patients with AVMs, especially if the lesion involves the cortical surface. Of patients presenting with hemorrhage, 30% have a history of epilepsy. Lesions close to the Rolandic fissure are particularly likely to present with seizures. About 10% of patients present with neurological deficit. This typically includes cognitive deficits and memory problems. However, some patients develop gradual weakness or visual loss.

Large AVMs, especially those involving the basal ganglia, may present with a slowly progressive dementia, hemiparesis or visual field defect, probably as a result of a "steal" effect, in which blood is shunted away from functional cerebral areas. The infrequent brain stem AVM may also produce a motor or sensory deficit, with or without cranial nerve involvement. Attacks of well localized headaches (unilateral and throbbing) occur in a proportion of patients subsequently shown to have a large AVM. Auscultation, especially over the eyeball, occasionally reveals a bruit.

Capillary vascular malformations are initially pale with normal overlying skin texture but may darken as the patient ages. Nodularity and a darker purple pigmentation may occur in adulthood due to increasing dilation of the dermal vessels. AVMs may demonstrate increased warmth, audible bruits, palpable thrills, or visible pulsations. Hypertrophy of the involved limb or structure may be apparent.

Other problems to consider when doing the work-up for AVMs, include Kasabach-Merritt syndrome, vein of Galen malformation, and Sturge-Weber syndrome. Kasabach-Merritt syndrome is a capillary hemangioma associated with platelet consumption resulting in thrombocytopenia and progressively enlarging vascular malformations which may involve large portions of their extremities. Bleeding commonly develops in the first year of life, secondary to chronic disseminated intravascular coagulation triggered by stagnant blood flow through the tortuous abnormal vessels. Anemia is caused by red cell damage as blood passes through deformed vessels of the tumor.

The vein of Galen is located under the cerebral hemispheres and drains the anterior and central regions of the brain into the sinuses of the posterior cerebral fossa. Aneurysmal malformation of the vein of Galen (a type of AVM with a dilated Galenic system serving as the venous outflow for an adjacent adenoma) typically results in high output congestive heart failure in neonates resulting from the decreased resistance and high blood flow in the lesion, or this may present later with developmental delay, hydrocephalus, and seizures.

Angiomatosis affecting the facial skin, eyes, and leptomeninges produces the characteristic features of the Sturge-Weber syndrome, which is characterized by capillary nevus over the forehead and eye, epilepsy and intracranial calcification. There is no clear pattern of inheritance. Practically all cases are sporadic, and many are associated with occipital AVMs. Epilepsy occurs in 75% usually presenting in infancy. Hemiparesis, homonymous hemianopia occur in 30%, and behavioral disorders with mental retardation occur in 50%.

Most AVMs are evident on CT scan unless masked by the presence of an intracranial hematoma. A double dose of intravenous contrast may aid visualization, especially with small lesions. Following IV contrast, streaks of enhancement representing dilated feeding and draining vessels, irregular lesions strongly enhancing with contrast, and calcification may be apparent. Conventional MRI will clearly demonstrate the AVM, with associated signal change within or around the lesion from areas of old hemorrhage or gliosis. MRI is the investigation of choice in identifying cavernous vascular malformations (a rare, often congenital disorder of the venous system in which the hemangioma is a mass resembling a tumor, consisting of large blood-filled spaces which can occur at any site in the body). These are often missed on unenhanced CT scanning because it may be isodense with the surrounding brain. Most lesions show marked signal

change around this lesion due to a rim of hemosiderin deposition. Four-vessel angiography confirms the presence of an AVM and delineates the feeding and draining vessels. Occasionally small AVMs are difficult to detect and only early venous filling may draw attention to their presence. In the presence of a hematoma, angiography should be delayed until the hematoma resolves, otherwise local pressure and surrounding hemorrhage may mask demonstration of an AVM. If the angiogram is subsequently negative, then MRI is required to exclude the presence of a cavernous malformation.

Patients presenting with AVMs pose the clinician with difficult management choices. First, there is no consensus as to how AVMs should be classified or even defined. The natural history of an AVM is hard to predict. There are three disciplines, surgery, interventional radiology and radiation therapy, all offering their own treatments and with some disagreement as to which treatment modality is superior.

The various methods of treating AVMs all risk further damage. The urgency of the patient's clinical condition and the risks of treatment must be weighed against the risk of a conservative approach. Indications for intervention include: 1) expanding hematoma associated with the AVM, 2) progressive neurological defect, and 3) high risk of hemorrhage especially in younger patients (with many years of future risk), with the AVM less than 3 cm in diameter and in a non-eloquent site. "Eloquent" is a term used to indicate that the anatomic brain location is very important for vital neurological functions such as movement, language, and memory. Non-eloquent refers to brain areas that can be injured or removed without significant functional neurological deficit. Operative removal may not benefit epilepsy control.

Methods of treatment include operation (excision), stereotactic radiotherapy, embolization, and occlusion of feeding vessels. Complete excision of the AVM (confirmed by pre- or postoperative angiography) is the most effective method of treatment. Image guided surgery may aid localization of small AVMs or cavernous malformations. Some deeply situated lesions in the basal ganglia or brain stem are inoperable in view of the risk of neurologic deficit.

Standard radiotherapy is of no value in the treatment of AVMs, but focused beams either from multiple cobalt sources or from a linear accelerator, can obliterate up to 80% of lesions under 3 cm in diameter within two years of treatment. Results are far less encouraging for larger lesions, although combinations of embolization and stereotactic radiotherapy may provide an alternative treatment method for large inoperable AVMs in the future. Although avoiding direct operative damage, stereotactic irradiation destroys tissue locally at the target site. The larger the dose, the greater the chance of AVM obliteration, but the greater the risk of neurological deficit from local tissue destruction. A further disadvantage is the possible delay of up to two years before obliteration occurs. Despite this, stereotactic irradiation may prove ideal for some deeply situated lesions.

Skilled catheterization permits selective embolization of feeding vessels with isobutyl-cyanoacrylate, although this technique is not without risk. Embolization alone is unlikely to produce complete obliteration, but if used preoperatively, it may significantly aid operative removal. Occlusion of feeding vessels, whether by direct operation or by an endovascular balloon, fails to prevent persistent filling of the AVM because of the development of collateral vascularization.

Prognosis varies greatly with severity and presentation. Vasospasm and delayed ischemic complications rarely develop. Generally speaking, small AVMs are a greater risk of bleeding than larger lesions. The risk of initial and recurrent bleeding over a 5-year period in patients with a previously unruptured AVMs is approximately 15% (i.e. 2-3% per year); however, the risk increases to 50% over 5 years for lesions under 3 cm in size. After hemorrhage, the chance of a further bleed is slightly increased in the first year but beyond that, the risk reverts to that of an unruptured AVM. In contrast to the high mortality following aneurysm rupture, hemorrhage from an AVM carries the relatively low mortality rate of approximately 10-20%.

Questions

1. True/False: AVMs represent abnormal embryonic and fetal morphogenesis during the retiform stage of development of endothelial channels (approximately day 48 of human embryogenesis).

2. All of the following are used in the treatment of AVMs except:
   a. Excision
   b. Stereotactic radiotherapy
   c. Embolization
   d. Cryotherapy
   e. Occlusion of feeding vessels

3. True/False: The rare AVM that produces a very enlarged "vein of Galen aneurysm" can cause heart failure in infancy as a result of large volume blood flow through the shunt.

4. True/False: Occipital AVMs are frequently associated with hemangiomas of the face (Sturge-Weber syndrome).

5. True/False: The decision to treat an individual patient with an AVM requires balancing the natural history of the disease and in particular, the risk of hemorrhage against the risk of an interventional procedure.

6. True/False: Significantly decreased perfusion pressure is uncommon in areas adjacent to an AVM.

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Answers to questions

1. True 2. D 3. True 4. True 5. True 6. False

Chapter XIX.1. Fractures
Annemarie Uliasz

This is a 13 year old male who presents to the emergency department with a chief complaint of right forearm pain. While playing soccer earlier that day, he patient fell onto his right hand and heard a snapping sound. He reports that the pain in his forearm increases with movement. It is visibly swollen and deformed.

Exam: VS are normal except for a resting tachycardia secondary to pain. He is alert and cooperative, but subdued, in moderate pain. His head, neck and torso, show no signs of external trauma. Heart, lungs and abdomen are normal. Upper extremities: Swelling and deformity is observed at the right mid-forearm, corresponding to his area of greatest pain. Radial pulses and sensation are intact.

An IV is started and he is given 3 mg of IV morphine. AP and lateral radiographs of his right forearm demonstrate displaced, angulated fractures of the radius and ulna with overriding (overlapping) ends. An orthopedic surgeon is consulted. The patient is sedated and given additional analgesia. A closed reduction is performed with good alignment of the radius and ulna. Immobilization is accomplished with a fiberglass cast extending from the hand to the proximal humerus.

The skeletal system of children is anatomically, biomechanically, and physiologically different from that in adults. The presence of growth plates (or physes) in the pediatric skeleton is one major difference. The growth plate is composed of cartilage. It can be thought of as the "weakest link" in the pediatric bone. It may separate before an adjacent joint ligament tears. Injuries to the growth plate may result in deformities.

Another difference seen in children is a thicker periosteum surrounding the bones. As a consequence, fractures in children tend to be more stable and less displaced than those seen in adults. The greater bone-forming potential of the pediatric periosteum results in faster bone healing in children. Non-unions are rare in pediatric fractures.

A third difference is the increased porosity, due to larger, more abundant Haversian canals, and decreased density of pediatric bones. This feature makes children's bones more prone to buckling when compressed, or bowing when bent.

Finally, remodeling is more rapid in children than in adults. Imperfect reductions have been known to remodel into satisfactory alignment. The differences between pediatric and adult fractures result in different fracture patterns, problems of diagnosis, and management techniques.

Description of a pediatric fracture includes the anatomic location and configuration of the fracture, as well as, the relationship of the fracture fragments to each other and to the adjacent tissue. The anatomic location of the fracture can be described as diaphyseal (involving the central shaft of a long bone), metaphyseal (involving the ends of the shaft of a long bone), physeal (involving the growth plate), or epiphyseal (involving the ends of a long bone).

There are several configurations unique to pediatrics that may describe the fracture. A plastic deformation occurs when the bone is bowed beyond elastic recoil, without an actual fracture. This is called a bowing fracture (most common in the ulna) when the bone appears to be bent without any fracture line evident. A buckle fracture (or torus fracture) occurs due to axial compression of bone at the metaphyseal-diaphyseal junction. These fractures are inherently stable and heal within 2-3 weeks with immobilization. A greenstick fracture occurs when a bone is angulated beyond the limits of plastic deformity. The force of impact was insufficient to cause a complete fracture. Instead, there is a fracture on the tension side and plastic deformity with an intact cortex and periosteum on the compression side. A complete fracture describes a fracture in which both sides of the bone are fractured. Complete fractures may be subclassified according to the direction of the fracture line. A transverse fracture line is at 90 degree angle to the long axis. A spiral fracture line encircles a portion of the shaft and is oblique in orientation. Oblique fracture lines are 30-40 degrees to the long axis. A fracture site revealing multiple fragments is comminuted and is unusual in children.

The relationship of fracture fragments to each other can be classified by the extent of displacement. Angulation describes the angle of deviation between the pieces of bone at the fracture site. Translocation describes transposition of segments of bone. Impaction occurs when one fracture surface is driven into the opposing fracture surface. Overriding describes the slipping/overlapping of either part of a fractured bone past the other.

The relationship of the fracture fragments to the surrounding tissue can be classified as open or closed. In an open fracture (also called compound fracture), a break in the skin is present due to penetration of the skin by a fracture fragment from within or because a sharp object has penetrated the skin to fracture the bone. An open fracture increases the risk of infection. The skin is intact over the fracture site in a closed fracture.

The Salter and Harris system is used to classify growth plate injuries. Physeal injuries are classified into five groups:

Type I: Fracture through the physis without involvement of the metaphysis or epiphysis. A non-displaced type I fracture is not visible on X-ray, but a displaced type I fracture can be identified because the epiphysis and metaphysis will not be aligned.

Type II: A fracture through the physis and metaphysis, with a fragment of the metaphysis remaining attached to the physis.

Type III: A fracture involving the epiphysis and the physis.

Type IV: A fracture involving the epiphysis, physis, and metaphysis.

Type V: The physis is crushed (compressed) without fracture of the epiphysis or metaphysis.

Generalized prognostic information regarding risk for premature physeal closure and indications for treatment can be determined according to the Salter and Harris classification. Type I and type II fractures can be treated with cast or splint immobilization. They do not require perfect alignment and have an excellent prognosis. Type II fractures of the distal femur are an exception, however. Unless anatomic alignment is attained by closed or open techniques, these fractures have a poor prognosis. Type III and type IV require precise anatomic reduction to minimize future joint or growth abnormalities. Type V fractures are usually recognized in retrospect as a consequence of premature physeal closure. Prognosis is poor due to premature growth cessation.

With knowledge of the most common types of injury for a child's developmental level, a physician may predict the type of injury sustained. Fractures in the newborn and infant are frequently the result of child abuse. In young children, falling onto an outstretched hand is a common mechanism of fracture. As a consequence, upper extremity and clavicle fractures have a greater incidence than lower extremity fractures. Bicycle and motor vehicle accidents are often the cause of fractures in children approaching the teens.

Analgesia may be administered to reduce the child's pain and anxiety during examination of the injury. Before palpation, the skin must be examined for breaks. The neurovascular status of the limb must be assessed prior to and after splinting and reduction. Although it is not necessary to palpate the site of an obvious fracture, palpation of adjacent or distant areas may be required to determine if more than

one fracture may exist. A baseline motor examination should be completed. Assessment of the joints above and below the injury should be included.

Prior to obtaining radiographs, the limb should be temporarily immobilized to minimize soft tissue trauma and improve patient comfort. Views in the anteroposterior and lateral planes, are required. An oblique view may be necessary in areas such as the elbow or wrist. Comparison views of the opposite limb may be helpful in distinguishing growth plates from fracture lines (2).

Open fractures carry a high risk of infection. Debris should be removed immediately. Pressure applied with a sterile pressure dressing will control hemorrhage. The limb should be splinted. The wound should be irrigated with saline and covered with saline-soaked sponges. Intravenous antibiotic prophylaxis, usually a first-generation cephalosporin should be initiated. Tetanus prophylaxis should also be administered (3).

Operative treatment under general anesthesia is required for approximately 4-5% of pediatric fractures (1). Indications for surgical stabilization include displaced epiphyseal fractures, displaced intra-articular fractures, unstable fractures, fractures in the multiply injured child, and open fractures. Three basic techniques are used in the surgical management of pediatric fractures: open reduction and internal fixation (ORIF), closed reduction and internal fixation, and external fixation. Open reduction refers to intraoperative surgical reduction of the fracture ends, while closed reduction refers to manipulating the fracture externally to achieve reduction. Internal fixation refers to the insertion of metal pins, screws, plates or other hardware to stabilize or fixate the fracture once reduction is achieved, while external fixation refers to fixation of bones by splints, plastic dressings, or transfixion pins. Casts are sometimes considered external fixation but they are usually referred to as external support.

Open reduction and internal fixation may be required for displaced epiphyseal fractures (especially Salter-Harris types III and IV fractures, intra-articular fractures, and unstable fractures). Other indications include neurovascular injuries requiring repair, failure to obtain anatomic alignment, and occasionally, open fractures of the femur and tibia.

Closed reduction and internal fixation is indicated for specific displaced epiphyseal, intra-articular, and unstable metaphyseal and diaphyseal fractures. Common indications include supracondylar fractures of the distal humerus, phalangeal, and femoral neck fractures. Multiple closed reductions of epiphyseal fractures may cause repetitive damage to the physeal germinal cells, and are therefore contraindicated.

The clavicle is the most frequently fractured bone in children (4). The most common site of fracture is between the middle and outer thirds. Clavicle fractures can be the result of birth injuries in newborns but are more typically the result of a fall on an outstretched arm in older children. The diagnosis is easily made by physical and radiographic evaluation. The patient will have pain with shoulder and neck movement. Crepitus and local swelling may be present. Neurovascular injury is rare. An AP radiograph of the clavicle is usually sufficient for diagnosis. Clavicle fractures in the newborn require no further treatment. A palpable callus can be detected several weeks later. In older children, a sling or shoulder immobilizer (a sling with another strap holding the horizontal forearm portion against the torso) is used to elevate the upper extremity to reduce downward pull on the distal clavicle. Figure-of-eight clavicle straps which extend the shoulders to minimize the overlap of fracture fragments, may also be used, but most patients find this uncomfortable and there is no clinical advantage over a sling or shoulder immobilizer. A palpable callus can be detected several weeks later which remodels in 6-12 months. Clavicle fractures usually heal rapidly in 3-6 weeks.

Proximal humerus fractures are usually the result of a fall backwards onto an extended arm. Neurovascular injury is rare. However, axillary nerve damage should be suspected if the patient experiences abnormal deltoid function and paresthesia or anesthesia over the lateral aspect shoulder. Treatment includes immobilization by a sling-and-swathe (a broad elastic bandage holding the humerus against the body) for 3-4 weeks. Because of the significant remodeling potential of this area, a certain amount of deformity is acceptable. Fractures with extreme angulation (greater than 90 degrees) may require surgical reduction.

Supracondylar fractures (distal humeral metaphyseal region proximal to the elbow) are the most common elbow fracture in children (4). They occur most frequently between the ages of 3 to 10 years old. This fracture is often the result of a fall onto an extended arm. The patient will hold the arm in pronation and resist flexion because of pain. Neurovascular injury is common in severe displacement. Because flow through the brachial artery can be affected, this injury should be treated as an acute emergency. Swelling, if severe, can block venous and arterial structures. A careful neurovascular examination is necessary. Compartment syndrome of the volar forearm can develop within 12-24 hours. Volkmann's contracture due to intracompartmental ischemia may follow (5). Pins are often used to fix the fracture after closed or open reduction. The more common less severe supracondylar fractures without neurovascular compromise can be splinted with the elbow in a position of comfort flexed at 90 degrees, and the forearm splinted in pronation or neutral position.

Lateral humeral condyle fractures are the result of falls in which the radial head drives into the capitellum of the humerus. An oblique shearing fracture of the lateral joint surface occurs. There is usually severe swelling even though the fracture appears small on X-ray. There is a high risk of malunion and nonunion in these fractures. Because both the growth plate and the joint surface are displaced, open reduction and fixation with percutaneous pins may be required. A cast without pinning may be satisfactory for non-displaced fractures.

Radial head (proximal radius) fracture is often associated with other elbow injuries. Radial head fractures are common and can often be diagnosed clinically since they may be difficult to see on X-rays. Patients with radial head fractures have most pain with supination/pronation while having mild pain with flexion/extension of the elbow. The radial neck may angulate as much as 70-80 degrees. Angulation of 45 degrees or less usually remodels spontaneously. Closed manipulation is required in larger degrees of angulation.

Forearm fractures are a common result of falls. If both bones are involved, one bone may be completely displaced with the other bone only suffering a greenstick fracture. Closed reduction and casting are used in the treatment of stable fractures. Closed intramedullary pinning and open reduction and internal fixation are operative options for unstable fractures.

Torus (or buckle) fractures of distal radial metaphysis are common. They are usually the result of a minor fall onto the hand with wrist in dorsiflexion. The fracture is impacted and there is minimal soft tissue swelling or hemorrhage. There is usually a minor distal ulna fracture associated with these distal radius fractures. Treatment is by a short-arm cast. Fractures typically heal in 3-4 weeks.

A Salter-Harris type I fracture frequently occurs through the distal radial physis. Unless the epiphysis is displaced, it will not be visible on X-ray. Thus, it must be diagnosed clinically. Any patient with a suspected distal radius fracture, presenting with tenderness over the distal radial physis should be presumed to have a non-displaced Salter-Harris type I fracture. They should be placed in a splint and followed clinically 2-3 days later. These injuries are commonly mistaken for wrist sprains. If at follow-up, the distal radius is non-tender, then a fracture is unlikely. However, if tenderness over the physis persists, then a fracture is likely and immobilization should be continued and referral to an orthopedic surgeon is appropriate.

The Monteggia injury is a fracture of the mid or proximal ulna associated with a dislocated radial head. The radial head should be pointing at the capitellum in all views. Such ulna fractures are often large, obvious and distracting making it easy to miss the dislocated radial head. Whenever a mid or proximal ulna fracture is noted (including olecranon fractures), critically inspect the alignment of the radial head with the capitellum. It is likely that a Monteggia injury occurs with many mid and proximal ulna fractures. Closed reduction of the radial head dislocation is necessary in addition to reduction and casting of the ulna fracture. Chronic elbow motion may be lost if the radial head dislocation is not properly reduced.

Phalangeal fractures in children are usually the result of crush injuries, such as slamming a finger in the door or a hyperextension injury from a basketball. If the distal phalanx is involved there may be a painful subungual hematoma which can be drained for pain relief. Occasionally, the growth plate is involved (Salter-Harris type II). Treatment is usually by splint immobilization. Closed reduction is rarely necessary; however, if there is angulation or malrotation, it may be required.

Carpal bone fractures are uncommon in children. As in adults, scaphoid fractures may be occult and difficult to identify on X-rays. Tenderness over the scaphoid (the floor of the anatomic snuff box) should indicate the possible presence of a scaphoid fracture even if X-rays fail to demonstrate a fracture. A thumb spica splint should be applied so that the thumb and wrist are immobilized. The blood supply to the scaphoid is injury prone, which puts the patient at risk for avascular necrosis and chronic pain. Scaphoid tenderness should be splinted aggressively. If the scaphoid is non-tender in a few days, then a fracture is not likely; however, persistent tenderness suggests the possibility of a fracture and referral to an orthopedic surgeon is appropriate.

Pelvic fractures are the result of major blunt trauma. Treatment is usually symptomatic due to the thick periosteum which confers stability. The patient should be assessed for intra-abdominal injuries.

Hip fractures are usually due to motor vehicle crashes, bicycle crashes, or falls from heights (4). Patients present with pain on gentle hip movement. There is a greater risk in children for avascular necrosis and growth cessation or deformity due to the vascularity and presence of a physis. Femoral neck fractures are unstable. They are treated with open or closed reduction and internal fixation to stabilize the fracture.

Femoral shaft fractures are the result of high-energy trauma. In younger children, the possibility of abuse must be considered. In children under 3 years old, approximately 70% of femur fractures are non-accidental (i.e., inflicted) (4). Although most femur fractures are closed, bleeding into soft tissues of the thigh may result in significant blood loss. Femoral shaft fractures may shorten and angulate due to longitudinal muscle pull and spasm. Length restoration and alignment are attained by longitudinal traction. Overgrowth of approximately 1.0 to 2.5 cm is commonly seen in femur fractures in children between 2-10 years old. Casts are used in this age group to allow for some shortening. Perfect reduction is unnecessary because remodeling is so rapid. A solid union is usually attained within 6 weeks.

Non-displaced oblique tibial fractures can occur in children less than 3-4 years old (toddler fracture) as the result of a rotational injury sustained while running or playing. Clinical features include pain, unwillingness to bear weight, and refusal to walk. Physical exam may be difficult to locate the site of the injury except for a refusal to bear weight on the affected lower extremity. The fracture may be radiographically subtle. Careful inspection of AP, lateral and sometimes oblique radiographs may identify the fracture. Evidence of new bone formation may be seen radiographically within 1-2 weeks, and requires an additional 2 weeks of immobilization. Large distal tibia fractures (as opposed to small subtle ones as in the toddler's fracture) in young children are more likely to be associated with intentional injuries as in child abuse.

Ankle fractures may involve the medial or lateral malleolus. Medial malleolus fractures are uncommon. In children, a Salter-Harris type I fracture of the distal fibular physis cannot be confirmed radiographically so it must be suspected clinically based on tenderness over the physis. These fractures are difficult to distinguish from ankle sprains. If a fracture is suspected, they should be placed in a splint. Ankle sprains are far more common than fractures in older children and adolescents. The Ottawa ankle rules have been validated as a decision tool for ordering ankle X-rays in adults. These rules probably work for children as well, but validation data for children have yet to be presented. The rules indicate that radiographs should be ordered if there is swelling or tenderness of either of the malleoli, or inability to bear weight after the injury.

Foot fractures can occur in the tarsal bones, metatarsals and/or the phalanges. Fractures of the metatarsal shaft are usually the result of direct trauma to the foot resulting from a fall, bicycle, or sledding injury. Injury is followed by soft tissue swelling and, sometimes, ecchymosis. Palpation reveals tenderness directly over the fracture. Fifth metatarsal tuberosity fractures (dancer's fracture) are also common and consist of an apophyseal avulsion fracture at the peroneus brevis tendon insertion. Swelling, ecchymosis, and localized tenderness to the fifth metatarsal tuberosity suggests a fracture. Contraction of the peroneal musculature increases the tenderness.

Toe phalangeal fractures are common and are usually the result of direct blows. They usually occur when the child is barefoot. The toes are swollen, ecchymotic, and tender. Mild deformity may be present. Closed reduction is not indicated unless the toe is significantly displaced. Casting is not usually necessary. Adequate alignment can be achieved by "buddy" taping the fractured toe to an adjacent stable toe.

Questions

1. Why do pediatric fractures heal faster than adult fractures?
2. How is a fracture described?
3. How is external fixation different from internal fixation?
4. What is the most frequently fractured bone in pediatric patients?
5. What kind of fracture is sustained in a toddlers fracture?
6. How can a toddler's fracture be distinguished from child abuse?
7. What other injury is commonly associated with a mid or proximal ulna fracture?
8. Name at least three fractures that are difficult to identify on X-rays and must often be diagnosed clinically?

Related x-rays

Salter-Harris examples: Yamamoto LG, Chung SMK, Inaba AS. Salter-Harris. In: Yamamoto LG, Inaba AS, DiMauro R. Radiology Cases In Pediatric Emergency Medicine, 1994, volume 1, case 18. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v1c18.html

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Multiple cases of fractures (see index and table of contents): Yamamoto LG, Inaba AS, DiMauro R. Radiology Cases In Pediatric Emergency Medicine, 1994-2002, volumes 1-7. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/pemxray.html

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Answers to questions

1. Fractures in children heal more rapidly than those in adults because the pediatric bone has a thicker periosteum and more efficient remodeling.

2. A fracture is described by its anatomic location, configuration, relationship of the fracture fragments to each other, and relationship of the fracture fragments to the surrounding tissue. Physeal fractures can be described according to the Salter-Harris system.

3. External fixation refers to fixation of bones by splints, casts or transfixion pins. A cast is sometimes considered merely external support, rather than external fixation. Internal (or intraosseous) fixation is stabilization of the bone fragments by direct fixation to one another with surgical wires, screws, pins, rods, or plates.

4. The clavicle is the most frequently fractured bone in the pediatric population.

5. A toddler's fracture is a subtle non-displaced spiral fracture resulting from a rotational injury while running or playing.

6. A toddler's fracture is subtle and non-displaced, while a large distal tibia fracture is more likely to be associated with severe trauma (not just falling while walking) or child abuse.

7. Radial head dislocation (the Monteggia injury).

8. a) Non-displaced Salter-Harris type I fracture of the distal radius, b) scaphoid fracture, c) radial head fracture, d) Non-displaced Salter-Harris type I fracture of the distal fibula (lateral malleolus).

Chapter XIX.2. Splinting
Erick M. Itoman

This is a 7 year old female who presents to the clinic with a chief complaint of left wrist pain. She was rollerblading with several friends, and was accidentally pushed from behind. She fell forward with outstretched, pronated arms. She denies hitting her head, loss of consciousness, vomiting, and abdominal pain.

Exam: VS T37.0, P105, R20, BP 117/75. She is comfortable, alert and appears to be in no distress. Mild abrasions are noted on her left knee and palmar surfaces of both hands. No obvious puncture wounds are present. She has mild discomfort upon palpation of her left knee, but she is able walk, stand, and jump without difficulty or discomfort. Her right wrist is normal, but tenderness is elicited upon palpation of her left distal radius. Slight wrist swelling is noted, but no angular deformity is present. The remainder of her exam is unremarkable.

Radiographs reveal a non-displaced distal radius fracture of the left wrist without angulation. She is placed in a forearm sugar tong splint, and her mother is given instructions to follow-up with an orthopedic surgeon.

Splints are used to temporarily immobilize fractures, subluxations, sprains or soft tissue injuries. Other indications for splinting include acute arthritis, severe contusions and abrasions, skin lacerations or burns across joints, tendon lacerations, tenosynovitis, animal bites, deep space infections, joint infections, and puncture wounds (1). The goal of splinting is immobilization to minimize pain and prevent further damage to nerves, vessels, muscle, skin, etc. (2). Immobilizing tender joints, as seen in tenosynovitis, hemarthrosis, or acute arthritis, reduces pain and inflammation. Abrasions and lacerations that cross joints can be stretched open if the extremity is not immobilized. Regardless of the initial event, tissue damage results in inflammation. Immobilization of the injured limb minimizes irritation and reduces edema (1). Immobilization of fractures reduces the risk of further displacement, minimizes hemorrhage, soft tissue damage, and risk of neurovascular injury.

All injuries that present with immobility, pain with movement, swelling, reproducible pain on palpation, anatomic deformity, discoloration, or crepitus should be evaluated with appropriate radiographic studies (3). Severe musculoskeletal injuries need immediate orthopedic consultation. These injuries include open fractures, fractures with neurovascular compromise, fractures that are too deformed, angulated, or displaced to adequately splint, and any dislocation that cannot be reduced in the ED. Pediatric patients with sprains warrant special attention. A Salter-Harris type 1 injury may not exhibit any radiographic evidence of a fracture, and may present like a sprain. All children who present with tenderness over the physis (growth plate) of a long bone should be presumed to have a Salter-Harris type 1 fracture injury and immobilized in an appropriate splint (3). The presence of a non-displaced Salter-Harris type 1 fracture is identified clinically during the follow up examination. Persistent tenderness several days after the injury implies the presence of a fracture (to be confirmed by additional radiographs which may show new born formation 7 to 10 days after the injury). Rapid resolution of tenderness implies the absence of a fracture.

The two categories of splints are classified based on their raw materials, plaster and fiberglass. Cardboard, aluminum and other semi-rigid or malleable materials can also be used for temporary splints. Plaster splints are made from gauze material impregnated with plaster of Paris, which is made from gypsum. Gypsum, when heated, loses water and is reduced to a powder. When water is added, the gypsum-powder hardens as the calcium sulfate dihydrate molecules recrystallize (1). The reaction is exothermic and can possibly burn the patient, but most of the time, it just feels warm. Depending on the temperature of the water (hot water allows for a quicker set time) the plaster may take anywhere from 2-8 minutes to set. Although hard, the plaster takes about a day to reach its maximum strength. Plaster has the distinct advantage of molding to the individual's anatomy, but it can be messy and difficult to work with (1). An upper extremity injury may require anywhere from 8-10 layers of plaster while the lower extremity may take 10-20 layers (4). Despite the large amount of material used, plaster is still relatively inexpensive (1). Once the plaster is set, water must be avoided. Excessive water will cause the crystallization to become unstable, making the splint soggy. The newer fiberglass splint materials comes prepackaged with padding. The prepackaging reduces the steps needed to prepare the limb prior to splinting, but increases the cost. The padding also absorbs water and sweat well, minimizing the accumulation of moisture (1). Fiberglass has several other advantages over plaster. It is lighter, stronger, has a quicker set time, and is not as messy as plaster. The fiberglass hardens in minutes and cures in approximately 10-20 minutes (1,4). Fiberglass, because of its prepackaged nature, does not mold to the individual's anatomy as well, so kinking may occur where the splint is bent to fit the limb (4). Kinks, although small, may be a potential sight of irritation causing skin breakdown and pressure injury.

The procedure for splinting should always start with a general inspection of the limb. Abrasions, cuts, and lesions need to be cleaned and dressed. Next, the limb should be rechecked for signs of compartment syndrome and neurovascular compromise. The splint width should be approximately half as wide as the circumference of the extremity. The following steps in the procedure will vary based on the type of split used.

For plaster splints, the plaster strips should be measured and cut to length. Since the splint is used to support the limb, the posterior surface is usually used as a measuring guide. Strips should be cut to a length slightly longer than needed. This will allow the splint to be folded upon itself to provided a smooth edge. A longer length will also allow for contraction of the plaster as it crystallizes (4). Optionally, stockinette (tube sock) can be rolled over the limb and cut to a length slightly longer than needed. The stockinette should look as if a long sock with an open hole has been placed over the extremity. Take time to smooth out the stockinette to prevent pressure spots and kinks at flexion creases. Also, make sure the stockinette is positioned so that there is extra material both proximal and distal to the area to being splinted. Cast padding (e.g., Webril cotton padding rolls) should be rolled over the extremity in a distal to proximal direction. If stockinette has been used, then the cast padding is rolled over the stockinette. Each successive roll of cast padding around the extremity should cover the previous roll by approximately 50-60% (4). This will ensure a double layer of padding over the area to be splinted. Make sure that the "extra" stockinette distal and proximal to the area being splinted is not covered with cast padding. Extra padding should be placed over the bony prominences and the fracture site. This will minimize pressure and discomfort. The plaster should now be immersed in water. The warmer the water, the quicker the plaster will set. With children, the water should be on the cooler side. The plaster will heat up as it hardens, and this may scare and burn a child but this is unlikely. Place the wet plaster on an open towel. Remove excess water, smooth the plaster, then apply the strip to the extremity. Adjust and position the plaster accordingly while smoothing to the contour to the patient's anatomy. While the plaster still soft, fold the proximal and distal ends of the plaster back over itself to provide a smooth edge. If a stockinette is used, fold it over itself, the cast padding, and the plaster. A smooth padded edge should be present at both ends of the splint. An optional cast padding layer can be applied over the splint to prevent the soggy plaster from

incorporating into the elastic wrap applied in the next step. Roll an elastic bandage over the outside of the extremity, usually in a distal to proximal fashion, securing the plaster to the extremity. Keep the limb in the desired position until the plaster thoroughly hardens.

Water soluble fiberglass splints involve fewer steps. Fiberglass splint materials come encased in cast padding material rather than as bare sheets of fiberglass. Once the limb has been inspected, and the proper splint width and length are selected, cut the length needed and place the fiberglass splint in water. The warmer the water, the quicker the fiberglass will harden. Remove the fiberglass splint from the water, and place it on a dry towel. Removed the excess water from the fiberglass splint by rolling it in a dry towel and applying pressure to remove water from the fiberglass. This can be repeated until the outside of the fiberglass splint material feels dry. Because the fiberglass is prepackaged, it has enough padding to be directly applied, but stockinette and additional cast padding can be optionally applied over the whole extremity, or just over the bony prominences (4). Once the fiberglass is placed over the extremity it should be molded to the desired shape. The padding material should be stretched over the end of the fiberglass to prevent the sharp fiberglass ends from poking the patient. An elastic bandage should then be applied to secure the fiberglass splint in place (4).

The final step in any splitting procedure should be to check the extremity for signs of neurovascular compromise. Capillary refill should be brisk, and sensation to light touch and pin prick should be intact. The patient should also be able to move the distal anatomy with minimal discomfort.

The patient and or parents need to be advised of the complications of splinting. In fracture cases, where swelling is prominent, the limb may expand in girth. Because the splint is not a rigid cylinder, the elastic wrap permits some expansion due to extremity swelling preventing harmful circumferential pressure by the splint. Nevertheless, neurovascular injury may occur and produce signs such as tingling, numbness, increasing pain, and/or paresis which may indicate the development of a compartment syndrome. If any of these signs or symptoms develop, the patient should be counseled to return to the emergency department immediately. Preventative measures should be taken such as limb elevation and periodic monitoring of the distal anatomy (1). Finally, the patient should be instructed to keep the splint clean and dry. Moisture will soften the skin and the splint, promoting itching, infection, pressure sores, and cast breakdown. Any discomfort on the skin could suggest pressure sores. The patient should be given instructions for follow-up with a contact number in case of complications.

Some common extremity splints include the following examples. Cast padding is applied to the extremity (stockinette optional), the splint material is applied as noted below, and an elastic bandage is rolled on over the extremity such that the splint material properly molds to the shape of the extremity without pressure spots.

Long Arm Posterior Splint (3). Indicated for elbow and forearm injuries, and/or immobilization. The elbow should be flexed at approximately 90 degrees to a position of comfort, and the forearm should be medially rotated 90 degrees (such that the volar side of the forearm is toward the body) with slight dorsiflexion at the wrist. If splinting a supracondylar fracture, position the forearm in a slightly pronated position. The splint should extend from the metacarpophalangeal joint to the upper arm, just distal to the axilla. The splint will be applied on the ulnar surface of the wrist and forearm and extend to the posterior surface of the upper arm.

Posterior Ankle Splint (3). Indicated for ankle sprains and non-displaced fractures of the ankle, foot, and distal fibula. The ankle should be in the proper anatomic position, flexed at approximately 90 degrees. The splint will extend distally from the foot (plantar side of the metatarsal phalangeal joints) to the proximal lower leg (level of the fibular head near the knee), and provides support to the posterior leg and foot. The splint should not impinge on the popliteal fossa when the leg is flexed. The patient should be given crutches (if the child is old enough to use crutches), otherwise encourage light weight bearing or non-weight bearing on the splint.

Ankle Stirrup Splint (also called ankle sugar tong splint) (3). Indicated for injures to the ankle, and ankle immobilization. Unlike the posterior ankle splint, the ankle stirrup splint provides lateral and medial support. The ankle stirrup splint provides superior immobilization for a fracture near the ankle compared to the posterior ankle splint. The splint is folded into a U-shape stirrup. The splint will wrap from the lateral surface of the calf (just distal to the knee), around the plantar aponeurosis and heel, to the medial surface of the calf just distal to the knee. Ideally, wide splint material should be used so that the bottom of the "U" will support the heel to the metatarsal phalangeal joints on the plantar side of the foot. The ankle should be flexed at 90 degrees (the same as for the posterior ankle splint).

Volar Forearm/Wrist Splint (1). Indicated for minor fractures near the wrist, soft tissue injuries to the hand and wrist, and fractures of the carpals and metacarpals. Extend the splint from the metacarpal heads of the palm to the volar surface of the forearm proximal to the elbow. The forearm is placed in the neutral position and the wrist should be slightly dorsiflexed. The palmar end of the splint should be rolled so that the hand can rest in a flexed position over the roll.

Ulnar Gutter Splint. Indicated for fractures of the 4th and 5th metacarpals. The splint material is folded on its long axis such that the ulnar side of the forearm fits into the long gutter formed by the splint. This should extend from the distal 5th finger or metacarpal to the proximal forearm (just distal to the elbow).

Forearm Sugar Tong Splint (3). Indicated for distal radius, wrist, and forearm fractures. Prevents supination and pronation of the wrist, flexion/extension of the forearm, and blunt trauma to the fracture site. This type of splint provides superior immobilization compared to the volar forearm and ulnar gutter splints. Extend the splint from the palmar aspect of the MCP joints, around the elbow, and to the dorsal aspect of the MCP joints. The thumb should be unopposed, and the remaining digits should be allowed 90 degrees of flexion. Flex the elbow approximately 90 degrees to allow a position of comfort. The volar surface of the forearm should be facing the body. The palmar end of the splint should also be folded over (i.e., rolled) to allow the fingers to rest in a flexed position over the roll.

Thumb Spica Splint (3). Indications include a nonrotated, nonangulated, nonarticular fracture of the thumb metacarpal or proximal phalanx. This type of splint can also be utilized for ulnar collateral ligament injuries, and scaphoid tenderness (fracture or suspected fracture). A thumb spica splint is often placed together with a volar wrist splint for suspected scaphoid fractures. The radial aspect of the forearm is placed in the splint so that the splint can form a long U-shape down the length of the splint (similar to the ulnar gutter, but on the radial side). The U-shaped splint will extend from the thumbnail to the mid-forearm. The thumb will be encircled by the distal part of the splint (with the tip of the thumb exposed) to completely immobilize the thumb, and as the splint extends proximally it will open wider to receive the radial surface of the forearm and wrist. The thumb should be slightly abducted and the wrist should be slightly dorsiflexed.

Questions

1. What are the common indications for splinting?
2. What is the purpose of splinting?
3. What are the complications involved with splinting, and how should these complications be evaluated by the patient?
4. Should sprains be splinted in a pediatric patient?
5. Briefly compare and contrast plaster and fiberglass splints.

6. What conditions warrant an orthopedic consult prior to splinting?
7. When choosing a splint strip size, what is the general rule of thumb?
8. What temperature of water should an inexperienced person use when splinting?
9. What is the first step in splinting?
10. What are some reasons for preferring splinting over casting?

Related x-rays/images

Ankle splint: Inaba AS. Ankle Injuries: A Sprained Ankle ? In: Yamamoto LG, Inaba AS, DiMauro R. Radiology Cases In Pediatric Emergency Medicine, 1995, volume 3, case 3. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v3c03.html

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Answers to questions

1. Splints are generally used to temporarily immobilize fractures, subluxations, or soft tissue injuries such as ankle sprains.

2. Splints immobilize the extremity, reducing damage to the nerves, vasculature, muscle, and skin. This will minimize edema and pain. Splints also stabilize fractures and prevent further displacement of subluxations.

3. If the splint is too tight it will compress the swollen extremity causing decreased sensation, paresthesia, and pain. The patient should be educated to check for brisk capillary refill, mobility of distal anatomy, numbness, tingling, burning, and increased pain. The immobility of the joint may cause contractures. Mobility of the distal anatomy should be evaluated. Stiffness of the immobilized joint should be expected. Wrinkles in the splinting material may cause pressure sores and skin breakdown, especially over bony prominences. Skin breakdown often starts with burning or itching, and may progress to ulceration.

4. Conservative treatment involves splinting of the extremity. The general rule is, when in doubt, splint. Splinting is indicated with sprains overlaying an open physis, because of the similar presentation to a Salter-Harris type 1 fracture. However, many sprain injuries (ankle sprain is the best studied example), will improve faster with gentle activity compared to total rest or immobilization.

5. Plaster is inexpensive and it allows for anatomic molding. However, it is relatively heavy and it can take longer to set and cure. Fiberglass is a more expensive, prepackaged, strong and light splint that cures quickly, but does not allow exact anatomic molding. For example, for an ankle fracture, plaster splinting results in a heavy splint, compared to a fiberglass splint which is stronger and lighter.

6. Complicated fractures include open fractures, fractures with any neurovascular compromise, fractures that are too deformed/angulated/displaced to adequately splint, and any dislocation which cannot be reduced in the ED.

7. The strip should be approximately 50% of the circumference of the extremity.

8. Cold water slows the curing process in both plaster and fiberglass, but ROOM TEMPERATURE water rather than cold water should be used. Warm water is best avoided since it will add further heat to the exothermic reaction.

9. Inspection. Wounds must be cleaned and dressed. Neurovascular compromise should be ruled out, and documented.

10. Casting forms a rigid cylinder over the extremity. In the first 24 hours following a fracture, swelling within the cylinder may result in vascular compromise (i.e., compartment syndrome). Splinting initially, then casting later is associated with fewer complications compared to early casting. Additionally, if the extremity is already swollen and a cast is applied, the fit of the cast will be loose once the swelling resolves. Casts are generally applied by orthopedic surgeons who are not always available for minor fractures. Splints provide an immediate means of immobilizing the extremity and do not require the immediate presence of an orthopedic surgeon.

Chapter XIX.3. Scoliosis
Robert C. Durkin, MD

A 12 year old girl is referred to the office with a chief complaint of "back looks funny". Her mother noticed the deformity incidentally when her daughter tried on swimsuits at the mall approximately 1 month prior to the visit. The patient did not notice any deformity herself. Previous examinations on annual visits for school did not mention a spinal deformity. Her mother also reports that her child has been growing rapidly for six months, but she has not begun her menses.

PMH is unremarkable.

ROS: She denies back pain, headaches, difficulty urinating or making bowel movements, numbness or tingling in the extremities or weakness. No abnormal skin rashes or birthmarks are appreciated. She denies shortness of breath, palpitations, fatigue or malaise. Frequent bleeding or bruisability is denied. No endocrine abnormalities are reported.

FH: Family history is significant for adolescent-onset scoliosis in a maternal aunt. No treatment was recommended. Pertinent review with the mother regarding family history is negative for short stature syndrome, neurofibromatosis, bone dysplasia, neoplasia, hereditary neuromuscular disease or other syndromes.

Exam: VS are normal. Standing height 152 cm (60 inches), weight 41 kg (90 lbs). Her mother's standing height is 165 cm (65 inches). She is an active and vibrant young girl. Her standing station (erect, feet together) demonstrates a level pelvis and level shoulders. Her gait shows smooth reciprocal heel-toe foot placement. Her forward bending test demonstrates right thoracic rib prominence with rotation of ribs 8 degrees at mid thorax by scoliometer. Her extremities show normal symmetric range of motion of all joints. No leg length discrepancy is present. Pulses are full and equal. Her neurologic exam is intact.

Imaging: Standing posteroanterior radiographs of the thoracolumbar spine are obtained. These images demonstrate an S-shaped curvature across the thoracic and lumbar spine. The larger curve magnitude measures 25 degrees by Cobb angle. Risser stage is 0.

Clinical course: You reassure the family that the condition is not life threatening but recommend follow up in 6 months. Repeat radiographs and examination are planned. The family moves out of state for one year after your initial examination. The patient returns to your office for check up 15 months after your initial visit. She has no back pain or complaint except rib prominence on forward bending. Examination shows her height is 163 cm (64 inches). Rotation on forward bending approaches 12 degrees at the mid-thorax. Neurological examination is normal. Her shoulders and pelvis are level. She began her menses 6 months ago. Radiographs show an increase in her curve magnitude to 32 degrees by Cobb angle. She is now Risser stage 2. Due to her progression by radiographic criteria and relative skeletal immaturity, you recommend a brace to control the curve. The child is compliant with the brace and wears it 23 hours a day for 12 months. No progression of the curvature is noted with brace treatment. At skeletal maturity, she has a well-balanced spinal deformity. Maximal curve magnitude is 28 degrees. She is active in sports and reports no pain.

Idiopathic scoliosis is the most common type of scoliosis. Scoliosis is characterized by lateral curvature of the spine on two-dimensional radiographs. In truth, the deformity is three-dimensional and rotation is a critical component. By definition, the etiology is unknown and the diagnosis can only be made after all other causes of spinal deformity have been excluded. The true prevalence in society is unknown and estimates are dependent on the method of measurement. By radiographic criteria (Cobb angle greater than 10 degrees), the prevalence is approximately 2-3%. For curves greater than 20 degrees, the prevalence drops ten-fold to approximately 0.3%. Females are predominately affected. Boys tend to have smaller curves and are less likely to progress. The female to male ratio is 1.4 to 1 for curves 11 degrees to 20 degrees. The ratio increases to 5:1 for curves greater than 20 degrees.

Idiopathic scoliosis is often divided by age of onset. Infantile curves are noted from birth to 3 years. Juvenile curves are recognized between 4 and 10 years. Adolescent curves are diagnosed after 10 years of age.

The family history is positive for scoliosis in approximately 30% of cases suggesting that inheritance has some role. Recognition of scoliosis in a family member is not helpful for determining curve magnitude or risk of progression. Inheritance patterns (sex-linked, autosomal dominant or recessive) are debated. Hormonal interactions and growth alterations have been implicated but are also controversial (1). Rapid growth is associated with curve progression, but this does not explain how the deformity initiates. Biomechanical forces must play a role as larger curves and the unbalanced spine tend to progress more than small well-balanced curves. Disorders of the connective tissue and matrix proteins are also suspect. The most viable hypothesis relates to abnormalities of the vestibular and equilibrium systems in the central nervous system. Disorders of equilibrium are probably the most widely supported as the cause of idiopathic scoliosis (2,3).

The diagnosis begins with a complete history. Back pain should be well characterized with respect to severity and duration as the presence of pain may suggest an irritant focus such as infection or tumor (4). Radicular signs, numbness, changes in bowel or bladder habits, tingling in the extremities or perineum imply a neurologic origin. Any history of trauma should be investigated thoroughly. Information regarding skeletal maturity may be helpful to determine the risk of progression and, therefore, one should inquire about menstrual history and sexual development (Tanner staging).

The physical examination begins with inspection from the back. The patient is standing with her/his feet together. Palpation of the tops of the iliac crest will assess pelvic tilt and leg length discrepancy. Screen the spine for midline dimples or cutaneous changes as these findings suggest a defect in the underlying spine. The "Forward Bending Test" is routinely used to screen for spinal deformity. The child is asked to bend forward at the waist with her hands clasped together. The head and arms are allowed to hang dependent in a relaxed manner. Inspection from the rear allows the examiner to sight tangentially down the spine. Attention should be paid for asymmetry of the rib or trunk height. Rotation of the spine is reflected in prominence of the ribs on the convexity of the curve. A Scoliometer (trademark) is an inclinometer used to measure trunk rotation in degrees. Each level of deformity should be measured (thoracic, thoracolumbar, and lumbar).

Objective measurement of spinal deformity begins with a standing posteroanterior (PA) radiograph of the entire thoracolumbar spine. The image is taken on a long cassette (36 in) to include the thoracic and the lumbar spine on one view. PA imaging is used to limit the radiation exposure to the breast and thyroid in an adolescent female. The Cobb angle can be determined by measuring the horizontal (transverse plane) endplate of the most tilted vertebrae at each end of the curve. The angle formed by the perpendicular to these two endplates is measured. True scoliosis is defined as a structural curvature of the spine with a Cobb angle greater than 10 degrees. Curves below 10 degrees should be labeled "minimal spinal curvature" as they represent positional curves and will likely regress spontaneously. For true scoliosis, radiographs are repeated every six months until skeletal maturity. Thereafter, annual rechecks are recommended until stability is confirmed.

Monitoring ossification of the iliac apophysis on radiographs can assess skeletal maturity. Normal ossification begins laterally and progresses medially as the child matures. By dividing the crest into quadrants, five stages of maturation can be assigned according to the system of Risser. Complete ossification requires approximately one year. Risser stages 0 - 2 imply relative immaturity. Risser stages 3 - 5 suggest that spinal growth is nearly complete.

Idiopathic scoliosis is diagnosis of exclusion. Scoliosis can result from congenital, irritative, neuromuscular, degenerative, and traumatic causes.

Congenital scoliosis is the product of the failure of formation or segmentation of spinal elements in prenatal life. Irritative curves are due to infections or neoplasms. Neuromuscular curves develop due to muscle imbalance in children with encephalopathy, spina bifida, or myopathies. Degenerative curves are seen in adulthood and result from biomechanical failure of the arthritic spine. Trauma can result in scoliosis if the injury weakens the integrity of the spine by fracture or dislocation.

Accurate knowledge of the natural history of a disease is mandatory for determining appropriate management of patients. The natural history of spinal curvature in the skeletally immature is different from expectations for curves presenting after spinal growth ceases. The probability of curve progression is the primary consideration when planning treatment (5,6).

Progression of spinal deformity is known to be associated with growth (7). Therefore, determination of skeletal maturity is often helpful in predicting risk of progression. The onset of puberty is associated with a rapid increase in spinal growth velocity. Menarche occurs after the peak velocity has been reached (8). For girls, the end of spinal growth corresponds to Risser stage 4. For boys, spinal growth can occur after Risser stage 4 and is less well defined. The risk of curve progression is higher for a child in Risser stage 0 - 2 compared to a child in Risser stage 3 - 5.

Larger curves at presentation are at higher risk of progression. The probability of progression greater than 10 degrees by Cobb angle is 67% for curves 40 -50 degrees. The corresponding probability for curves 20 -30 degrees is 30% (7). Thus, for young patients with scoliosis, the major factors determining risk of progression are skeletal maturity, curve magnitude, and curve type. Optimal interval of follow-up is determined by the ability to detect a real difference in the curve magnitude by Cobb angles. A widely accepted estimate of error in measurements of Cobb angles is approximately 5 degrees (9). During the peak velocity of spinal growth, the curvature may progress by 1 to 2 degrees per month. Therefore, rechecks should be scheduled every six months to allow sufficient time for a true change in the curvature to be detectable (greater than 5 degree error). More frequent follow up should be scheduled if rapid curve progression is noted.

Most patients with an established diagnosis of idiopathic scoliosis do not require treatment. For minor curves (less than 25 degrees) or the mature patient, examination and radiographs are repeated twice a year to monitor the curve. If the risk of progression is high due to curve magnitude and skeletal maturity, a brace is often recommended. The goal of bracing is to prevent progression. In fact, the brace does not attempt to correct or to improve the magnitude of the curvature with any lasting effect. Correction in the brace should be greater than 50% to achieve its goal. Bracing is used in a carefully selected patient to achieve a curvature under 30 degrees at skeletal maturity. The effect of the brace is dose-dependent. Therefore, the current recommendation is for the brace to be worn 23 hours a day for optimal results. Compliance can be a problem even with appropriate counseling (10-12). Physical therapy regimens and electrical stimulation have not been shown to affect the natural history of adolescent idiopathic scoliosis (12).

Surgical indications are based on many factors including the curve type, skeletal maturity, and curve magnitude. Documented progression on radiographs or parameters that suggest a high risk of progression must also be noted. In general terms, the immature patient who presents with a curve beyond the limits of effective bracing (greater than 40 - 50 degrees) or who has demonstrated significant progression despite effective bracing is a candidate for fusion. Standard techniques have evolved considerably over the last fifteen years. Instrumentation uses a combination of rods, hooks, and screws to correct the spine over individual segments. The ability to straighten the spine and maintain that correction until effective fusion occurs is tremendous. Depending on the specific characteristics of the patient, different approaches can be used. The standard posterior spinal fusion requires a long fusion construct. Anterior approaches allow a shorter construct and maintenance of flexibility by saving spinal segments. Thorascopic and laparoscopic techniques are being developed to allow microinvasive approaches to instrument and fuse the scoliotic spine (13).

Overall, the prognosis is favorable (14,15). Progression in adulthood is generally much slower than in adolescence. Curves less than 30 degrees at maturity are unlikely to progress. However, curves greater than 50 degrees have a 68% chance of progression. For curves between 50 and 75 degrees, the curves will progress by 1 degree per year. Therefore, surgical stabilization of the spine is recommended for curves greater than 50 degrees at skeletal maturity (5,6).

Mild to moderate idiopathic scoliosis in adulthood has no negative effect on pregnancy or delivery method. Generally, normal pulmonary function is found in patients with scoliosis. Restrictive pulmonary function does not occur until the curve reaches 100 degrees (16). No increased risk of mortality is found for adults with adolescent-onset idiopathic scoliosis (17). In most studies, the incidence of back pain does not differ significantly from the general population (4). Patients frequently note cosmetic concerns related to scoliosis. Severe psychological reactions to scoliosis are uncommon.

Questions

1. How is idiopathic scoliosis defined clinically and radiographically?
2. Who is more commonly affected - males or females?
3. As a diagnosis of exclusion, what other causes of scoliosis must be eliminated?
4. What physical findings are present in patients with scoliosis?
5. In the forward bending test, what physical finding suggests scoliosis?
6. What are the primary considerations when planning treatment?
7. What three forms of treatment are valid?
8. What is the long term prognosis for a patient with scoliosis in adulthood?

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Answers to questions

1. Clinical - side-to-side (sagittal) curvature of the spine. Radiographic - curvature of the spine whose curvature is greater than or equal to 10 degrees.
2. Females are affected more commonly than males.
3. Congenital, neuromuscular, traumatic, infectious, neoplastic, inflammatory, syndromic and degenerative causes.
4. Side-to-side curvature of the spine, rib hump, shoulder elevation, chest wall deformity, prominence of the scapula on one side.
5. Asymmetry of the rib hump
6. Risk of progression - skeletal maturity and magnitude of curvature.
7. Observation, brace, and surgery
8. Curvature less than 30 degrees - asymptomatic, non-progressive. Curvature greater than 50 degrees - progression in adulthood (1-2 degrees/year).

Chapter XIX.4. Osteomyelitis
Floyd S. Ota, MD

A 5 year old male presents with decreased appetite and intermittent tactile fever for the last five days. He complains of pain in his right leg and he has been having an increasingly difficult time walking over the last 2 days. He has a history of falling seven days ago. His mother denies reports of recent weight loss, cough, or dysuria. He has no previous medical problems.

Exam: VS T 39.4, P 110, R 16, BP 95/50, oxygen saturation 99% RA. He is alert and non-toxic appearing. His heart, lungs and abdomen are normal. Examination of his extremities reveals swelling, warmth and tenderness to his right proximal tibia. He has some palpable inguinal lymphadenopathy on the right. He has difficulty bearing weight and walks with a slight limp. There are no cutaneous skin lesions. His neurologic and joint exams are non-contributory.

Laboratory studies show WBC 18,000, 68% segs, 7% bands, 20% lymphs, 5% monos, H/H 13.4/40, Platelet count 290,000. ESR 60 and CRP 15. Plain radiographs of his right tibia and fibula are normal. An MRI scan shows a hyperintense signal in the marrow with a small pocket pus elevating the periosteum and soft tissue swelling of the right proximal tibia suggestive of osteomyelitis.

An orthopedic consultation is obtained, and a closed needle drainage of the area is done. IV vancomycin is started and subsequent blood and wound cultures grow out methicillin sensitive Staphylococcus aureus. His antibiotics are changed from vancomycin to oxacillin. While in the hospital, his fever declines and his function returns. He is discharged on oral antibiotics to complete four weeks of treatment.

Osteomyelitis by definition is inflammation of the bone. The annual incidence of acute osteomyelitis is about 1/5000 children under 13 years old (1). This disease appears to affect males more often than females, and the majority of the cases occur in patients less than 20 years old. The most common cause of osteomyelitis is bacterial; however, fungal and viral causes are also possible.

Acute bacterial osteomyelitis can be thought of in three different categories: 1) hematogenous seeding, 2) contiguous spread, and 3) direct inoculation of the bone either from surgery or trauma. Of the three categories, acute hematogenous osteomyelitis is the most common presentation in children. Acute hematogenous osteomyelitis has a predilection for the long bones of the body. Long bones consist of two distinct types of bone. The diaphysis or shaft is made of a dense lamellar bone, which is relatively acellular and slow growing. The ends of the bone near the growth plate (the metaphysis) is made of a maze like bone called cancellous bone. This maze like structure allows for spreading of the infection via small channels in the bone that leads into the subperiosteal space. It is here in the rapidly growing metaphysis that osteomyelitis often develops. The process begins when thrombosis and bacterial emboli transmigrate through the end capillaries as a result of local trauma or stasis of local blood flow. This results in bacterial seeding creating a nidus for infection that can be difficult to remove due to a relative lack of reticuloendothelial cells. Pus collects in the subperiosteal space and surrounding edema produces a mass effect that further decreases blood flow perpetuating tissue ischemia and necrosis. Isolated pieces of dead bone, or sequestrations can result from this process. As the remodeling process continues, an involucrum can be created when new bone is deposited over an area of dead bone. The pathophysiology of osteomyelitis differs slightly by age group. In neonates, blood flow from the metaphysis is continuous with the joint space and thus a concurrent septic arthritis may develop. Furthermore, in this age group the periosteum is thinner and thus more likely to rupture into surrounding tissue. This is in contrast to older children in which the infection is contained due to a well developed periosteum resulting in focal physical findings.

The signs and symptoms of acute osteomyelitis may be subtle, especially in the very young. The chief complaint of a child suspected of having osteomyelitis may be refusal to walk and bare weight on the affected limb, or the refusal to utilize a specific body part. Often a recent history of upper respiratory symptoms or trauma is elicited. The very young infant may present with only a history of a poor appetite and fever, or be ill appearing in fulminate septic shock. Objective findings are fever, swelling, point tenderness, and erythema of the affected body part. The child may have a pseudoparalysis of the affected limb. The most common long bones involved in descending order are the femur, tibia, humerus, fibula, radius and ulna (2). Flat bones are affected less than 20% of the time; of these the calcaneus and pelvic bones are the most common and about equal in incidence (2). Occasionally the physical findings are very subtle, such as a loss of natural body curvatures or normal skin creases. Thus, examination of the opposite side for symmetry is an important aspect of the physical exam. Lastly, assessment of the patient's gait for a limp may also help to make the clinical diagnosis.

Laboratory studies are helpful in making the diagnosis of osteomyelitis. The most useful laboratory values are the acute phase reactants, the erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP). These values are often highly elevated in the presence of acute osteomyelitis, and are non-specific indicators of acute inflammation. The ESR is determined by the rate that red blood cells fall through plasma. This value is dependent on the content of fibrinogen in the blood. The value for ESR usually starts to increase at about 48-72 hours from the start of the infection process. CRP is a protein created by the liver. The theoretical advantage to CRP is that it is said to rise earlier than the ESR, about six to ten hours after the onset of inflammation. It also declines much more rapidly after initiation of therapy, and thus may be a good way to monitor therapeutic efficacy (3). The white blood cell (WBC) count has been found to be unreliable in diagnosing acute osteomyelitis (4). Often, a normal WBC count may be misleading to the clinician in the presence of osteomyelitis. Despite this fact, a CBC can be helpful to rule out other diagnoses, and thus it is an integral part of the workup. Bacterial cultures, when positive, are very helpful in the diagnosis and management of acute osteomyelitis. Blood cultures have been reported to be positive 30-50% of the time (4). Sterile needle aspiration of the affected area yields an organism about 60% of the time if pus is attained (4). Identification of the offending organism and antibiotic sensitivities is an extremely important aspect to guide therapy. The most common organism isolated is Staphylococcus aureus (70-90%) (2). This is followed by group A Streptococcus, Streptococcus pneumonia, and Haemophilus influenza (2). Salmonella and other enteric pathogens must be considered in patients with sickle cell disease. In the newborn period, group B Streptococci, Escherichia coli, and Staphylococcus epidermis are often the cause of osteomyelitis. Lastly, Pseudomonas aeruginosa is a common cause of infection due to plantar puncture wounds that are sustained through sneakers.

Radiographic imaging is an important component in making the diagnosis of osteomyelitis, and should always start with plain radiographs of the affected area. Despite the fact that plain radiographs will only begin to show osteogenic changes five to seven days into the disease process, plain radiographs are helpful to rule out other etiologies of bone pain. A nuclear medicine bone scan is a very sensitive test to diagnose osteomyelitis. This procedure is done in three phases, and utilizes technetium 99m to create images that determine areas of infection and bone remodeling dependent on local blood flow. The sensitivity of the bone scan is high (>90%), and this test is often helpful when the exact location and extent of the infection in the body is unknown (5). CT scanning allows for three dimensional examination of bone and the surrounding soft tissues. This imaging modality can help to show periosteal reaction, cortical bone destruction and if any sequestration or involucrum is present (5). Ring enhancing soft tissue abscesses can also be found. Magnetic

resonance imaging (MRI) is an extremely useful imaging modality in acute osteomyelitis. Findings on MRI accurately illustrate the extent and structure of the area involved in the pathologic process. Sensitivity has been reported to be 88-100% with a specificity of 75-100% (5). Fat suppression sequences allow for better detection of bone marrow edema; however, this cannot differentiate between infection and inflammation (5). MRI may be the imaging modality of choice for infections involving the spine, pelvis, and limbs due to its ability to provide fine details of the osseous changes and soft tissue extension in these areas. MRI does have the disadvantages of high cost and requiring sedation for young children.

The differential diagnosis of a child who presents with fever, bone pain and tenderness includes rheumatic fever, septic arthritis, cellulitis, Ewing sarcoma, osteosarcoma, neuroblastoma, leukemia, thrombophlebitis, bone infarction due to sickle cell disease, and toxic synovitis.

The mainstay of treatment focuses on eradication of the offending organism and the minimization of tissue damage. The first is accomplished through initiating parenteral antibiotics. In the older child, the focus is against the more common gram positive organisms (S. aureus and group A Streptococci). A beta lactamase resistant penicillin (oxacillin, methicillin or nafcillin) or a cephalosporin will cover Group A Strep, but only 70% of Staph aureus. Thus, these antibiotics are unacceptable coverage since the risk of resistance is too high. All patients should be started empirically on vancomycin. In the younger child and patients with sickle cell anemia, gram negative pathogens such as Haemophilus and Salmonella must be considered, thus the addition of ampicillin or a third generation cephalosporin (cefotaxime or ceftriaxone) is important. The duration of treatment is somewhat controversial; however it appears that at least four to six weeks is required. Shorter courses have shown to have an increased incidence of recurrence (2). Peripherally inserted central IV catheters can be placed and home antibiotics can be arranged with home care. Recently, oral antibiotics have become an accepted option to complete therapy. However, the following criteria must be met: organism identification (with sensitivities), the ability to take and keep down oral antibiotics, a clear response to parenteral treatment, and assured routine compliance (4). Often, the dose of oral agents is two to four times the normal dose to maintain adequate drug levels. MIC and MBC (minimum inhibitory and minimum bactericidal concentrations) data may be useful in predicting a therapeutic success. Following laboratory results such as the CBC, CRP and ESR at routine intervals may be helpful to monitor clinical progress and monitor iatrogenic side effects.

Surgical debridement helps to decrease the tissue damage that occurs due to the inflammatory reaction caused by the infection. The removal of the inflammatory products allows for a more optimal environment to maximize the efficacy of medical therapy. Two criteria that help to make the decision to perform surgical debridement are the ability to aspirate pus from the lesion and a failure to see a clinical response within 36-48 hours of the initiation of medical treatment (4). Samples attained from debridement should be sent for pathology identification, cultures and antibiotic sensitivity.

Chronic osteomyelitis can occur due to a penetrating injury/inoculation or inadequate therapy (often due to non-compliance with outpatient antibiotics). This poses an extremely complicated medical and surgical task for the clinician. Like in acute osteomyelitis, Staph aureus is often the organism isolated by culture. However, chronic osteomyelitis has a higher incidence of gram negative rods, anaerobes, and non-bacterial pathogens such as fungus and yeast. Very long term antibiotic therapy and repeat surgical interventions may be required (with occasional amputation), and recovery is long and complication prone. The prognosis for a normal outcome with chronic osteomyelitis can be poor.

Questions

1. True/False: The most common pathogen in acute hematogenous osteomyelitis is Group A streptococci.
2. True/False: A sequestration is an area of loose necrotic bone that is a result of acute osteomyelitis.
3. True/False: The duration of antibiotic therapy for acute hematogenous osteomyelitis is typically 7-10 days.
4. True/False: Two clinical conditions for surgical intervention in acute osteomyelitis are the ability to aspirate pus from the lesion and a lack of response to medical treatment in 36-48 hours.
5. True/False: Plain X-rays will always show bony changes within the first few days of the onset of acute osteomyelitis.
6. True/False: The most common bone involved in acute hematogenous osteomyelitis in children is the tibia.
7. True/False: Osteomyelitis has a propensity to involve the diaphysis of the long bones.
8. True/False: Since Staph aureus is the most common organism involved in osteomyelitis, initiating therapy with an anti-Staph aureus penicillin such as oxacillin is generally accepted as adequate.

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Answers to questions

1. False. S. aureus is the most common. Group A strep is the second most common.
2. True
3. False. Typically the course is for 6-8 weeks, always starting with IV antibiotics and finishing with PO antibiotics if possible.
4. True
5. False. Plain films usually begin to show acute changes 5-7 days into the course of the disease process.
6. False. The femur is the most commonly involved bone. The tibia is the second most commonly involved.
7. False. The metaphysis is the most common site.
8. False. The rate of methicillin resistant S. aureus is too high to use oxacillin/methicillin as empiric therapy. Vancomycin should be initially started.

Chapter XIX.5. Septic Arthritis
Floyd S. Ota, MD

A 2 year old male presents with fever and refusal to walk for two days. He complains of pain and points to his right lower extremity. The pain has become increasingly worse, and he is unable to sleep at night. His appetite is decreased. There is a recent history of an upper respiratory tract infection about two weeks ago, but no recent trauma. The pain is not known to migrate. He has no past medical history but his immunizations are delayed (last immunizations at two months of age). There is no history of cough, headache, abdominal pain, vomiting, diarrhea, hematuria, or known tick exposure. Family history is negative for sickle cell disease and arthritis.

Exam: VS T 39.5, P 120, R 18, BP 100/50, oxygen saturation 100% in RA. Wt 10%ile, Ht 50%ile. He is thin appearing and refuses to walk. He is not fussy and nontoxic. HEENT exam is normal. His neck has good range of motion without pain. Heart, lungs, abdomen, and genital exams are normal. He is lying in a hospital bed with his right lower extremity externally rotated, abducted, and motionless. He has severe discomfort with minimal internal and external rotation of the right hip despite attempts to distract him. His other joints and neurological exam are normal. There are no notable skin lesions.

Laboratory studies show WBC 20,000, 80% segs, 10% bands, 8% lymphs, 2% monos, H/H 14/43, Platelet count 265,000. ESR 45. CRP 12. Serum glucose 95. UA SG 1.020, negative for blood. EKG normal sinus rhythm. Hip radiographs show widening of the acetabular space on the right.

An orthopedic surgeon is consulted. An arthrocentesis of the right hip is performed which shows WBC 110,000, glucose 35, gram stain shows many WBCs and few gram positive cocci. Surgical debridement of the right hip is performed. Empiric treatment with vancomycin and ceftriaxone is initiated after cultures are obtained. ASO, ANA and rheumatoid factors are negative. PPD and control is negative. Synovial fluid culture grows out Staph aureus sensitive to methicillin. Blood culture is also positive for methicillin sensitive Staph aureus. Vancomycin and ceftriaxone are discontinued and the patient is treated with oxacillin. Within three days of treatment onset, his fever declines and he slowly begins to ambulate. His appetite returns and he is eventually transitioned to high dose oral antibiotics to complete four weeks of treatment. He is discharged with home care physical therapy services.

Septic arthritis generally refers to bacterial infection of the joint space; however fungal and mycobacterium can also cause disease. Septic arthritis is a medical emergency and failure to provide prompt diagnosis and treatment may lead to severe morbidity and disability. The incidence is estimated to be 5.5 - 12 per 100,000 individuals (1). Septic arthritis is a disease primarily of young children in the first decade of life.

Diarthroidial joints have a synovial lining that separates the adjacent articular cartilages. This histologic lining is extremely vascular and lacks a basement membrane. This tissue produces synovial fluid, a viscous media that has an electrolyte and glucose concentration similar to that of plasma and acts as a lubricant to the adjacent cartilage. This fluid is normally sterile, but if invaded by bacteria, it provides a good environment for bacterial growth. The three main routes of joint infection are: 1) hematogenous (most common in children), 2) contiguous spread, and 3) direct inoculation from a procedure or trauma. The amount of blood flow to the synovium is high, equivalent to that of the brain. Thus, transient bacteremia can cause a large number of organisms to be delivered to this region. Bacteria normally cleared by synovial macrophages can be overwhelmed when presented with a large quantity of organisms. Proteolytic enzymes produced by bacteria and inflammatory cytokines incite damage to the articular cartilage. This process begins early in the infection, and its effects may render the articular surface susceptible to future degenerative joint disease. Furthermore, swelling of the joint capsule may predispose the femoral head to avascular necrosis due to ischemia of the capital femoral epiphysis. Dislocation or subluxation can also result from the increased intracapsular pressure (2). An important concept to emphasize is that the inflammatory process and tissue damage may progress despite the fact that the causative organisms have been eradicated.

Children with septic arthritis all present with one common feature, pain to the affected limb. This is due to stretching of the joint capsule from edema or an effusion. Joint pain may present as refusal to walk, to bear weight, or to utilize the affected limb. Often the children have fever and they can appear toxic to well appearing in their presentation. A history of trauma or upper respiratory infection in the weeks prior is sometimes elicited, which may mislead one from the true diagnosis of septic arthritis. Furthermore, septic arthritis may be a complication for patients with a history of recent surgery, urinary tract infection, and infection due to varicella zoster virus (due to secondary cutaneous infection of the lesions with Staph aureus or group A strep) (1).

On physical exam, swelling, tenderness, erythema, and warmth may be apparent to joints with little overlying tissue. However in a deep (well enclosed) joint such as the hip, these findings may be minimal to absent. Subtle findings such as a loss of natural body curvatures or normal skin creases may be all that is present. Thus, examination of the opposite side for symmetry is an important aspect of the physical exam. Range of motion is the most sensitive method to determine the presence of joint effusion (2). Children with septic arthritis often have significantly decreased and painful range of motion since any movement that stretches the joint capsule produces severe discomfort. In infants with septic arthritis of the hip, the classic physical finding is of a child lying motionless with his/her leg externally rotated and abducted. In septic arthritis of the axial skeleton and pelvis, direct compression of the joints may be the only way to produce clinical signs. It is important to examine all the joints of the lower extremities in a child with a limp, because the child may complain of knee pain, when in fact it is the hip that is affected. The most commonly affected joints are the knees and hips (67%). These are followed in incidence by the ankle, elbow, wrist and shoulders (1). Examination for signs of meningitis and performing a lumbar puncture when indicated is important in children who are susceptible to Haemophilus influenza, type B (but one would not necessarily know this until gram stain and/or culture information is available). One study found that 30% of children with septic arthritis due to this organism had concurrent meningitis (2). Haemophilus influenzae, type B (HiB) infections are currently almost nonexistent because of widespread effective HiB immunization. In the neonatal period septic arthritis often is present concurrently with acute osteomyelitis of the adjacent bone.

The differential diagnosis of a child with fever and joint pain includes: septic arthritis, transient synovitis, reactive arthritis, trauma, acute rheumatic fever, Henoch-Schonlein purpura, Kawasaki disease, serum sickness, lyme disease arthritis, inflammatory bowel disease, hematologic cancer, and connective tissue disease (i.e., juvenile rheumatoid arthritis, systemic lupus erythematosus, etc.). Toxic synovitis (also known as transient synovitis) of the hip is a viral or post infectious process causing acute arthritis that is important because it often causes a diagnostic dilemma for the clinician. Transient synovitis of the hip is often preceded by an upper respiratory tract infection or pharyngitis in previously healthy children. The peak incidence is 3-6 years of age (3). The etiology is unclear; however children with this condition may have a predisposition for hypersensitivity reactions. CBC, ESR and CRP studies are often (but not always) normal or only minimally elevated, and radiological studies often fail to show impressive changes. Rarely is joint aspiration performed, despite the

presence of a hip effusion if the clinical findings and laboratory studies are suggestive of this diagnosis. Toxic synovitis is a diagnosis of exclusion, and treatment consists of non-steroidal anti-inflammatory medications and bed rest. Overall prognosis is usually good (about 70% of patients have resolution of their symptoms within two weeks) (3), but avascular necrosis may occur in some patients.

Laboratory studies are helpful in diagnosing septic arthritis. The most useful laboratory values are the acute phase reactants, the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). These values can be elevated in the presence of acute septic arthritis, and are non-specific indicators of acute inflammation (Refer to the chapter on osteomyelitis for a discussion of CRP and ESR). A retrospective study found that patients with an ESR >20 combined with a fever >37.5, identified 97% of cases of septic arthritis and recommended joint aspiration if these values were present in a child with an irritable hip (4). The peripheral white blood cell (WBC) count is often obtained in the work up of septic arthritis. As a single value, it is unreliable to make the diagnosis of septic arthritis, or to rule it out. Despite this fact, a CBC can be helpful to rule out other diagnoses (such as leukemia), and thus it is an integral part of the workup. Joint aspiration is the most helpful test to make the diagnosis of septic arthritis. The synovial WBC count usually is greater than 80,000 with a predominance of segmented neutrophils. Glucose concentrations are decreased to about 30% of the serum glucose (2). This helps to differentiate septic arthritis from other etiologies of acute joint pain. Typically WBC count and glucose values are not as dramatically affected in cases of transient synovitis, reactive arthritis, and JRA. Bacterial culture and gram stain, when positive, are very helpful in the diagnosis and management of acute septic arthritis. Identification by gram staining is important because joint aspirates are sterile about 30% of the time in patients with septic arthritis (2). Identification of the offending organism and antibiotic sensitivities are an extremely important aspect to guide therapy. The most common organism isolated is Staphylococcus aureus (50%). This is followed by group A Streptococcus (25%), Streptococcus pneumonia (4%), and HiB (16%) (1). The percentage for HiB is probably substantially lower today because of widespread immunization. Neisseria gonorrhoeae (GC) should be considered in neonates and sexually active adolescents. GC septic arthritis may present with a polyarticular presentation, which is unusual for other causes of septic arthritis. Other pathogens to consider in the newborn period are group B Streptococci, and Escherichia coli. Recently, Kingella kingae has become a more recognized pathogen (1).

Imaging should start with plain film radiographs. When looking at the hip, AP and frog leg views should be obtained. The findings on plain radiographs that suggest septic arthritis are displacement of normal fats plains and widening of the joint space due to capsular swelling from an effusion. These signs are subtle and may not be present early on in the disease process. Ultrasound is a quick and noninvasive means of detecting the presence of a hip effusion. CT, MRI, and bone scans all have limited value in the diagnosis of straightforward septic arthritis. However, MRI and nuclear bone scan can help to differentiate between septic arthritis in the presence or absence of a concurrent osteomyelitis. Nuclear bone scans are also helpful when the foci of infection are unclear. All imaging modalities discussed above are able to detect the presence of a joint effusion, however none can differentiate between infectious and non-infectious causes of the effusion. Direct aspiration of the joint fluid is the most definitive means of diagnosis. Joint aspiration does not affect subsequent bone scan results (2).

Treatment of acute septic arthritis consists of surgical debridement and antibiotic treatment. The risk for poor prognosis is increased if any of the following factors are present: a delay in initiation of treatment, age less than six months, history of prematurity, the presence of S. aureus as the infectious etiology, and the presence of a concurrent osteomyelitis (5). Early intervention is required to minimize morbidity. Surgical arthrotomy for large joints is the rule; however this clinical intervention is not always indicated for involvement of smaller joints. The purpose of surgery is to produce an environment with minimal inflammatory products so that antimicrobial therapy is maximized. After surgical intervention, empiric parenteral antibiotic coverage for Staphylococcus aureus should be initiated. The drug of choice is vancomycin due to the high risk (currently about 30%) that the organism may be resistant to cephalosporins and methicillin (MRSA). Clindamycin is another choice that will cover most strains of MRSA, but it is not 100%, so vancomycin is preferred. A third generation cephalosporin should be added if the child is at risk for H. influenza or gonococcal disease. If CNS infection is suspected, meningitic doses should be implemented. The antibiotic regimen can then be narrowed once the cultures and sensitivities are received. As a rule, treatment duration is 3-4 weeks (6). Peripherally inserted central IV catheters can be placed and home antibiotics can be arranged with home care. Recently, oral antibiotics have become an accepted option to complete therapy. This can be done because antibiotic concentrations in the synovium are often higher than that of the serum due to slow reabsorption of the drugs (from the synovium). However, all of the following criteria must be met: organism identified and sensitivity to oral antibiotics is documented, the patient is able to take and keep down oral antibiotics, a clear response to parenteral treatment is demonstrated, and routine compliance is assured (2). Following the CBC, CRP and/or ESR at routine intervals may be helpful to monitor clinical progress and monitor iatrogenic side effects.

In conclusion, for straight forward cases of septic arthritis, the overall prognosis is good. Differentiating infectious from non-infectious etiologies of joint pain can be a clinical dilemma. The clinician must utilize a broad range of clinical tools to expeditiously diagnose and treat this condition so that outcomes are favorable.

Questions

1. True/False: Septic arthritis is a disease most commonly found in adolescent males.
2. True/False: In septic arthritis, the hips and knees are the most commonly affected joints.
3. True/False: In a child with septic arthritis of the hip, redness, swelling, and warmth are often detectable on physical exam.
4. True/False: Children with toxic synovitis never present with fever.
5. True/False: The ESR and CRP can usually distinguish between toxic synovitis and septic arthritis.
6. True/False: The most common bacterial etiology of septic arthritis is Staph aureus.
7. True/False: Haemophilus influenzae type B used to be a common cause of septic arthritis in young children, but this is very uncommon today.
8. True/False: Surgical arthrotomy is always warranted for cases of septic arthritis.

Related x-rays

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5. Chapter 5: Pediatric Orthopaedic Infections. In: Richards SB (ed). Orthopaedic Knowledge Update; Pediatrics. 1996, Illinois: American Academy of Orthopaedic Surgeons, pp. 35-46.

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Answers to questions

1. False. It is a condition that usually affects younger children early in the first decade of life.
2. True
3. False. The hip joint is deep and has a significant amount of surrounding tissue, thus inflammation may not be easily detected on physical exam. Exam findings may be subtle, such as asymmetry or loss of function. Decreased and painful range of motion is the best way to detect an effusion by physical exam.
4. False. They also can present with fever. This is why differentiating between toxic synovitis and septic arthritis can be a difficult clinical problem.
5. No definite answer here. Low ESR and CRP values make septic arthritis unlikely. Very high ESR and CRP values make septic arthritis more likely. Intermediate ESR and CRP values are not very helpful in distinguishing toxic synovitis from early septic arthritis.
6. True
7. True
8. False. In larger joints surgical intervention is almost always performed. However in cases of septic arthritis of smaller joints, medical management can be carried out with good results. Orthopedic surgical consult should always be obtained expeditiously whenever the diagnosis is considered.

Chapter XIX.6. Hip Conditions
Robert C. Durkin, MD

A 12 year old boy is brought to your office for evaluation of limping for one month. His parents cannot recall a specific episode of trauma. Further probing may correlate the limp to a fall from his scooter at home. His left distal thigh near his knee is sore with prolonged walking. He cannot run or jump without severe medial left knee pain. He has difficulty squatting or rising from a deep chair. Previous examinations of his knee by another physician were reportedly normal. He has been taking ibuprofen for a "bursitis" without improvement. His limp is getting worse.

PMH is significant for asthma, sleep apnea and severe obesity.

ROS: He denies any radiation of pain below the knee, paresthesias or tingling in the feet, back pain, morning stiffness, swollen joints, fevers, chills or recent infection. He has no symptoms of endocrine abnormalities or hypothyroidism.

FH: Significant for multiple individuals with severe obesity.

Exam: VS T36.8, P 80, RR 24, BP 130/76. He is extremely obese but in no significant distress. He has difficulty standing with both feet together and prefers to externally rotate his left foot. His gait is notable for his left foot turned outward. He has a truncal sway to the left side with the swing phase of his right foot. He cannot squat. His spine is straight. His neurological exam is intact. His knee examination is normal bilaterally. His left hip flexion is decreased to 40 degrees. He has obligate external rotation of the hip with attempted flexion. Internal rotation causes severe thigh pain. Internal rotation is essentially zero degrees. His pulses are full and symmetric.

Although his chief complaint relates to pain near his knee, your examination suggests that his problem is in his hip. AP pelvis and lateral views of both hips demonstrate a left slipped capital femoral epiphysis.

He is placed on crutches with toe touch weight bearing on the left side. He is referred immediately to an orthopedic specialist for consultation. The pediatric orthopedist admits him to the hospital for insertion of a screw to secure the unstable growth plate. He remains on crutches for six weeks after surgery. After six weeks, he is allowed to walk freely. Swimming is encouraged. Activity restrictions include no running or jumping (no sports) until the growth plate has closed radiographically. Complete closure can take six to eighteen months. Since the slip is mild, he has a good to excellent prognosis. Many years of productive activity can be expected. Due to the deformity, mild arthritis may occur in the fifth to sixth decade of life.

Limping in the child can be the result of a multitude of causes. A careful history is critical to narrowing the differential diagnosis. The physician must consider any information that may direct the investigation. Three questions to consider are: 1) Is it painful? 2) How old is the child? 3) What is the duration of symptoms?

Pain is not a specific complaint, but may help the examiner to localize the area of interest to a specific joint or limb. Absence of pain does not narrow the list of causes as infection and neoplasia can present with a painless limp.

The age of the child can narrow the differential diagnosis. Broad overlap can occur so one should not ignore a possible diagnosis just because it is not typical in a certain age group. Leg length discrepancy and neuromuscular conditions such as cerebral palsy can affect the gait pattern of a child at any age. In the toddler (age 1 to 4 years), primary consideration should be given to infectious causes such as septic joint or osteomyelitis. Non-infectious causes include transient synovitis, trauma, or a late presentation of developmental dysplasia of the hip (DDH). In the child/juvenile (age 4 to 10 years), infection and transient synovitis must be excluded. Trauma is common in this age group. Legg-Calve-Perthes disease (idiopathic avascular necrosis of the hip) or juvenile rheumatoid arthritis (JRA) may be first diagnosed at this age. Benign bone tumors can also cause limping in this age group. The adolescent (age 11-16 years) commonly limps due to trauma. Neoplasia may affect children in the second decade. Conditions affecting the growth plate such as slipped capital femoral epiphysis (SCFE) must be excluded in any adolescent presenting to the office with limp and hip, thigh or knee pain. It should be noted that hip pathology may deceptively present with thigh or knee pain. Thus, the hips must be thoroughly examined in patients presenting with thigh or knee pain.

Developmental dysplasia of the hip (DDH) may be diagnosed in any age group. The age of the child will determine the presenting signs and symptoms. In the newborn, DDH is identified by instability of the hip on initial examinations. In the ambulatory child, the dislocated or dysplastic hip will be evident by a limp, waddle, or leg-length difference on examination. Early recognition of the dysplastic or unstable hip is important so that treatment can be instituted before significant deformity occurs and at a time when sufficient growth remains to enhance hip development (1). If the diagnosis is missed, patients may present in late childhood or in their teen or adult years with severe degenerative damage to the hip.

The human hip begins as a continuous structure in the embryo. A cleft forms at the 7th week of development and the gross structure of the joint is formed by the 11th week. Growth of the hip joint is dependent on mechanical and genetic factors. The development of the acetabulum and the femoral head is dependent upon concentric reduction of the round ball in the cup. Dislocation of the femoral head from the acetabulum will cause deformity of both parts of the hip. Growth of the depth and width of the cup is determined genetically by the acetabular cartilage and the triradiate cartilages (2).

DDH is found in 1.0-1.5 per 1000 live births. Risk factors include female gender, first born child, and breech lie in pregnancy (1). A history of DDH in the family is also very significant as the incidence of DDH in parents of affected children is approximately 10 fold greater than the general population (3). Although the etiology is unknown, idiopathic, capsular laxity, hormonal, genetic, crowding, and syndromic causes have been proposed. Support for genetic relationships are noted by the 25 to 50 fold increase rate of DDH in American Indian and Polynesian populations (4,5). DDH is rarely seen in certain African populations or ethnic Chinese (6,7). Evidence for the crowding phenomenon is noted by the relationship of torticollis, hip dysplasia, oligohydramnios, and metatarsus adductus (8). Certain syndromes (Larsen syndrome and arthrogryposis) contain DDH as part of their constellation of findings.

Clinical findings are age-dependent. The newborn may have marked instability of the hip (9). The Ortolani maneuver involves dislocation and relocation of the hip. The palpable clunk associated with the relocation of the femoral head is often called the Ortolani sign. This Ortolani finding disappears as the soft-tissues around the dislocated hip become contracted in the first two-weeks of life. Similarly, the Barlow sign is likely present in the first few weeks of life, but this sign gradually disappears soon thereafter, making it imperative that a thorough examination of the hips be performed and documented several times during the newborn period. In the older child, limited abduction of the hip is the sentinel finding. In addition, the dislocated hip effectively shortens the thigh length giving the appearance of limb length discrepancy or the Galeazzi sign. The apparent thigh shortening often leads to dramatic asymmetry of the

gluteal skin folds. With regards to prognosis, hip stability (stable/unstable) and the resting position of the hip (dislocated/reduced) are important concepts to recognize. A newborn with an unstable but reduced hip requires treatment directed at maintenance of stability. More active intervention such as surgery is needed for the ambulatory child with a fixed dislocation (2).

Treatment must be directed in achieving a concentric reduction of the femoral head in the acetabulum, stability of the hip joint, and proper remodeling of the growth cartilages throughout childhood. Treatment algorithms are age dependent: birth to six months, six months to 18 months, and greater than 18 months. The risk of complications such as deformity, avascular necrosis, and arthritis increases directly with the complexity of the treatment regimen. In the infant (birth to six months), a flexible harness designed to hold the hips in a reduced position and allow some movement is the primary form of treatment. The Pavlik harness is the simplest and most commonly used harness in the United States. Success with the Pavlik harness can approach ninety-five percent. Pavlik failures are associated with bilateral dislocations, Ortolani negative hip, application of the harness after 7 weeks of age, and noncompliance (10,11). Although early success with the Pavlik harness can be expected to result in development of a normal hip in the majority of cases, late dysplasia can be found in 10-20% of adolescents or adults (12,13). Therefore, long-term radiographic monitoring must be maintained. For the child (six months to 18 months), closed manipulation and application of a body cast are often employed to reduce the dislocated hip. In the older child or juvenile, open surgical reduction of the hip with reconstruction of bone deformity of either side of the hip joint is often required. In the adult with untreated DDH, significant deformity of the hip will be present. The decision for reconstruction will depend on the magnitude of arthritis already present at the time of diagnosis. Whatever the age, the treatment algorithm for DDH should adhere to the following principles: avoid complications, obtain a concentric reduction, achieve a stable hip, and promote growth and remodeling of the hip joint.

Clinical Practice Guidelines for Early Detection of DDH (1)

Newborns:
All newborns are to be screened by physical exam.
Ultrasonography of all newborns is not recommended.
Use of triple diapers is not recommended.
If exam is positive, refer to an orthopedist (ultrasonography is unnecessary).
If exam is equivocal, repeat exam by pediatrician in 2 weeks.

2 week exam:
If positive, refer to orthopedist.
If suspicious, consider orthopedic referral or ultrasound at 4 weeks.
If negative, periodic exams with well baby visits.
Consider risk factors if suspicious or negative.

Risk factors and recommended actions:
Female: Follow periodicity schedule.
Positive family history (male): Follow periodicity schedule.
Positive family history (female): Optional future imaging.
Breech (male): Optional future imaging.
Breech (female): Recommend imaging (ultrasound/X-rays).

Legg-Calve-Perthes Disease (LCP disease) is commonly diagnosed in the juvenile patient (4-8 years old). The condition is characterized by limp, loss of hip internal rotation and abduction, and progressive deformity of the femoral head. The shape of the head, congruency of the hip joint, and range of motion of the hip at maturity determine long term prognosis.

LCP disease is more common in boys than in girls (5:1). The incidence of bilaterality is 10-15%. There is no evidence to suggest LCP disease is inherited. The disease is more common in certain geographical locations especially urban centers. Affected children are thought to manifest a specific psychological profile such as hyperactivity. In addition, 89% of those children affected have a delayed bone age. Ethnic variations show a higher risk in Japanese, Eskimos, and central Europeans while American Indians, Polynesians, and African Americans have a lower risk. Anthropometric studies document small stature in height and weight. Normalization of stature occurs in early adolescence. Growth abnormalities may represent alterations of growth hormone dependent somatomedin activity (14-16).

Although the etiology is unknown, most current theories involve vascular compromise to the femoral epiphysis. Two episodes of infarction are thought necessary to cause the changes consistent with LCP disease in humans. Increased blood viscosity, thrombophilia, and intraosseous venous hypertension have been proposed as mechanisms for vascular compromise (17-19).

The syndrome is typified by certain classic radiographic stages: initial, fragmentation, reossification, and residual phases (20). The femoral head deformity may occur in many ways. In general, softening of the femoral head marks the period of fragmentation. Synovitis and restricted hip motion lead to deforming forces that compress the femoral head. Deformity may also result from physeal arrest of the femoral epiphysis. Reossification of the deformed head fixes the abnormal shape. Potential for remodeling of the deformity is related to the age of onset as a younger child has more years of growth remaining to reshape the head. Therefore, age of disease onset is the second most important factor related to outcome, preceded only by residual deformity. In general, affected children younger than 8 years of age at onset have a better prognosis. Attempts to estimate risk of deformity and overall prognosis by radiographic criteria in the early stages of LCP disease have met with variable success (20-24).

The clinical presentation is most commonly an insidious limp. Although pain in the thigh or knee should prompt a thorough examination of the hip, pain is not a frequent finding in LCP. Physical examination is marked by limited abduction and internal rotation of the hip. Flexion contracture of the hip is an important finding. The Trendelenburg test, which tests gluteus medius strength, is often positive. It is done by standing behind the patient and checking that the pelvis is level. The patient is then asked to stand on one leg which should result in gluteus medius muscle contraction on the weight bearing side and the contralateral pelvis should elevate on the unsupported side, indicating that the gluteus medius muscle on the weight bearing side is working properly (negative Trendelenburg sign). A positive Trendelenburg sign is recognized if the pelvis on the unsupported side does not elevate.

Limb length should be measured as any significant discrepancy may predict a poor prognosis if due to head collapse. Imaging should begin with plain radiographs. Early in the disease course, the x-rays will show increased density of the femoral head. Progressive

fragmentation of the epiphysis will follow. Weakness of the bone may lead to collapse. With reossification of the femoral head, the deformity will become fixed in the new bone (25). Other modalities such as magnetic resonance imaging (MRI) and bone scan may be helpful in diagnosis and to direct treatment. Arthrography is often used to document true head deformity in the younger child especially in early phases of the disease (26). The differential diagnosis may be broad and careful selection of laboratory and radiographic studies should make the diagnosis clear. Specific consideration should be given to the following: transient synovitis, septic joint, osteomyelitis, trauma, hypothyroidism, multiple epiphyseal dysplasia, chondrolysis, Gaucher disease, hemophilia, juvenile rheumatoid arthritis, neoplasia, mucopolysaccharidoses, Meyer's dysplasia, or residuals of congenital hip dysplasia (27).

Treatment protocols abound (19,22,25,28-32). The primary goals in the treatment are to prevent deformity, to minimize growth disturbance, and to prevent degenerative joint disease. The critical concept is the containment of the femoral head in the acetabulum through the period of risk of deformity (19). The treatment remains controversial. Non-operative and operative advocates abound. Non-operative treatment requires maintenance of sufficient range of motion through therapy and bracing protocols. Surgical treatment is oriented toward redirecting the softened femoral head into the acetabulum to cover the vulnerable regions and to provide a mold for femoral head remodeling (25,32). For the hip that cannot be contained in the socket, sophisticated surgical techniques are used to treat pain, length discrepancy, and restricted motion. Well controlled studies with uniform treatment protocols in patients matched for age, gender, degree of head involvement, and other factors are needed to determine direct management of this complex disease in the future.

Slipped Capital Femoral Epiphysis (SCFE) remains one of the most common disorders affecting the hip in adolescence (33). This condition is characterized by a displacement of the femoral head through the physeal plate. Since the femoral head is held securely in the acetabulum, the femoral neck displaces anteriorly causing an apparent varus deformity of the proximal femur. Weakening of the perichondral ring associated with puberty leads to a separation of the physis through the widened zone of hypertrophy.

SCFE has been reported in 2 to 10 per 100, 000 population. Children with SCFE tend to be obese because this excess weight places excessive downward stress on the femoral epiphysis. Lower rates are seen in eastern Japan. Higher rates have been reported in African Americans and Polynesians (34,35). SCFE is more common in boys than girls (3:1). Boys are commonly affected between ages 9-16 years and girls are affected between 8-15 years of age.

Children with SCFE are usually obese. An antalgic gait or painful limp (Trendelenburg gait) with the foot turned outward is commonly seen. Knee pain is reported in 25-50% (36). Whenever knee or thigh pain is the chief complaint, the hip must be thoroughly evaluated since the pathology may be originating from the hip. Hip examination is notable for limited true flexion. Due to the deformity of the femoral head, the hip will turn in external rotation to prevent impingement of the femoral neck on the acetabulum with hip flexion (obligate hip external rotation with flexion). The hip has little or no internal rotation. For the acute slip, ability to bear weight may be limited.

The differential diagnosis includes trauma, infection, neoplasia, rheumatoid disease, avascular necrosis, congenital hip dysplasia or dislocation.

The goal of treatment is to prevent further displacement. The child should be restricted in his/her activity immediately after recognition of the problem. The child should remain non-ambulatory until the hip is stabilized. Preferably the child will be placed on bed rest or restricted to a wheelchair. A single screw is placed percutaneously to fix the slipped epiphysis in situ. Screw placement is guided by fluoroscopic imaging under anesthesia. A single screw is adequate fixation if properly placed (37). The patient is restricted to crutch assisted ambulation for 6-12 weeks after surgery. Corrective osteotomy may be planned for severe deformity. Due to the excellent long term prognosis for the hip, osteotomy should be delayed at least 2 years to allow bone remodeling (28).

Long term follow up data of patients with SCFE are available (28,29). In general, the prognosis is good to excellent. Mean hip activity scores were related to the severity of the slip. Degenerative arthritis is seen in almost all hips with moderate to severe slips. Two-thirds of mild slips had degenerative changes on radiographs at 41 years average follow up. Only one hip replacement surgery had been performed for this group over 41 years. Hips that were pinned in situ had less complications and higher activity scores than hips that underwent corrective surgery (29).

Complications such as avascular necrosis and chondrolysis can adversely affect outcome. Bilateral slipped capital femoral epiphysis can occur simultaneously or sequentially. Identifying those patients at risk for a slip on the contralateral asymptomatic hip is difficult. Children with endocrine disease (thyroid deficiency), renal failure, and previous radiation of the femoral epiphysis are at highest risk of bilateral slip (16,38).

Questions

1. What three questions should be considered in the limping child? Why?
2. What are three common causes for limping in the toddler? Juvenile? Adolescent?
3. What physical findings are noted in a newborn with DDH?
4. What physical findings are found in the toddler with hip dislocation?
5. What three factors are required for normal hip development to guide treatment for DDH?
6. What is the proposed etiology of LCP?
7. What are the four radiographic stages of LCP?
8. What factors influence the long-term prognosis most significantly for LCP?
9. What is the typical body habitus for a patient with SCFE?
10. What physical findings are present in SCFE?
11. What is the overall prognosis with proper treatment for SCFE?

Related x-rays

SCFE: Yamamoto LG. Thigh and Knee Pain in an Obese 10-Year Old. In: Yamamoto LG, Inaba AS, DiMauro R. Radiology Cases In Pediatric Emergency Medicine, 1995, volume 2, case 10. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v2c10.html

Challenging hip case: Yamamoto LG. Vomiting Following Reduction of Intussusception. In: Yamamoto LG, Inaba AS, DiMauro R. Radiology Cases In Pediatric Emergency Medicine, 1995, volume 2, case 13. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v2c13.html

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Answers to questions

1. Is it painful? How old is the child? What is the duration of symptoms? These three questions will help to narrow the differential diagnostic possibilities.

2. Toddler: transient synovitis, infection, trauma. Juvenile: trauma, transient synovitis/infection, Legg-Calve-Perthes disease. Adolescent: slipped epiphysis, trauma, neoplasia

3. Hip instability - Ortolani sign. Asymmetric gluteal skin folds.

4. Leg length discrepancy, Galeazzi sign (apparent thigh length difference), waddling gait.

5. Concentric reduction of femoral head, stability, remodeling and growth of acetabular cartilage.

6. Although the etiology is unknown (commonly stated as idiopathic), most current theories involve vascular compromise of the femoral epiphysis. Two episodes of infarction are thought necessary to cause the changes consistent with LCP disease in humans. Increased blood viscosity, thrombophilia, and intraosseous venous hypertension have been proposed as mechanisms for vascular compromise.

7. 1. Initial, 2. Fragmentation, 3. Reossification, 4. Residual.

8. Age of patient at onset and proportion of femoral head involvement. Children who have LCP disease before age eight have a better prognosis over children greater than eight years of age at time of onset. The proportion of head involvement forms the foundation for several classification schemes. Maintenance of the height of the lateral column of the femoral epiphysis appears to have the most prognostic significance in children in any age group. Whole head involvement or collapse of the lateral column by more than fifty percent carries a poor prognosis.

9. Obese, delayed maturation of skeletal age.

10. Trendelenburg gait or antalgic limp, obligate external rotation of the hip with flexion, limited internal rotation of the hip.

11. Good to excellent. High activity level. Slow degenerative process of the hip with few cases requiring prosthetic hip replacement.

Chapter XIX.7. Common Sprains and Dislocations
Brian T. Garcia

This is a 12 year old male who presents to your clinic with a 1 day history of pain and tenderness over his right ankle. He states that he stepped on someone's foot at basketball practice and "landed funny". It is painful to bear weight on his ankle, but he can do so if asked. He has been applying ice to the area since incurring the injury, with some relief of the pain.

Exam: VS are normal. His exam is unremarkable except for the right ankle, which is positive for moderate swelling and tenderness over the lateral malleolus. No ecchymosis or gross deformity is noted. Passive inversion and plantar flexion of the ankle produces pain. Anterior drawer test of the right anterior talofibular ligament is negative for gross laxity.

An X-ray of his ankle is obtained which does not reveal any fractures.

He is advised to rest the affected joint for today and is instructed to elevate his ankle and wear a compression bandage around the ankle. He is also instructed on performing pain-free range of motion exercises and light activity as tolerated.

The ankle is one of the most common sites for acute musculoskeletal injuries, with sprains accounting for 75 percent of ankle injuries (1). A sprain refers to stretching or tearing of a ligament. The most common mechanism of injury in ankle sprains is a combination of plantar flexion and inversion (1). The ankle joint is a hinge joint normally permitting movement in one plane (dorsiflexion and plantar flexion). In addition, up to 18% of axial rotation of the talus may occur within the tibial mortise (3). The lateral ligamentous complex consists of the three fibular collateral ligaments: the anterior talofibular ligament (ATFL), the calcaneofibular ligament (CFL), and the posterior talofibular ligament. These ligaments stabilize the ankle laterally, and are commonly injured in ankle sprains (2). The ATFL is the most commonly injured ankle ligament (4). Ankle sprains range in severity from grade I to grade III (1). Grade I refers to partial tearing of the ligaments. Grade II refers to partial to complete tear of the ATFL, and partial tear of the CFL. Grade III involves complete rupture of the ATFL and CFL (4).

History of the mechanism of injury allows the clinician to infer the pathologic status and structures involved (2). Patient will often report a twisting injury of the foot. The signs and symptoms of ankle sprains are varying degrees of pain, tenderness, and swelling over the lateral aspect of the ankle (4). Other signs are mild to moderate ecchymosis, loss of motion and function, and mechanical instability (1). Careful physical examination should include inspection, palpation, ability to bear weight on the affected ankle and special tests (1,3). Special tests include the anterior drawer test, which is used to assess the integrity of the ATFL. The inversion stress test is used to assess the integrity of the CFL (1). A positive "squeeze" test, which is occurrence of distal pain on compression of the fibula and tibia at the midcalf, may indicate the presence of a syndesmosis (the membranous ligamentous connections between the tibia and fibula) sprain (1). The positive findings of the affected ankle should be compared with the other, uninjured ankle (4). Traditionally, standard AP, lateral, and mortise views have been recommended in the evaluation of all cases of ankle injuries to rule out the possibility of occult fractures and osteochondral injuries and to assure articular congruity and alignment (2). The Ottawa Ankle Rules for obtaining radiographs of ankle injuries have modified this approach. These rules recommend radiographs if there is bony tenderness in the posterior half of the lower 6 cm of the fibula or tibia (i.e., lateral or medial malleolus tenderness), or inability to bear weight both immediately after the injury or during the medical examination (2).

The differential diagnosis of acute ankle sprains can include fibular fractures (lateral malleolus), tibial fractures, osteochondral fracture of the talar dome, peroneal tendon subluxation, congenital tarsal fusion, talar fractures, calcaneal fractures, and subtalar subluxation (4).

Early management of acute ankle sprains includes RICE (rest, ice, compression and elevation) (1). RICE and partial weight bearing are indicated as tolerated with optional crutches depending on the patient's ability to ambulate (4). Ibuprofen and/or acetaminophen may help with pain relief. Range of motion and gradual ambulation result in faster recovery compared to total rest (4). Surgery is indicated only in patients with recurring instability. Most patients have an excellent prognosis (4).

Nursemaid's elbow (also called subluxed radial head) is an injury which occurs when infants or children are lifted or pulled by the hand or arm. This pulling injury results in the radial head slipping through parts of the annular ligament resulting in the injury. Stubborn behavior (pulling away) may also cause this type of injury (4). This is one of the most common elbow injuries in young children between the ages of 1-5 years (4). The child may complain of pain in the elbow following a traction (pulling) injury. No significant swelling or angular deformity should be visible. They do not use their upper extremity and will hold their elbow at the side with their forearm on their lap (4). A classical physical exam finding of a nursemaid's elbow is refusal and pain with attempted forearm supination. Some parents may complain that the child has injured the wrist or shoulder, but in this age group, a pulling injury is most likely to affect the elbow. Physical examination of the infant may note point tenderness over the radial head, but this is not reliable (5).

The differential diagnosis of nursemaid's elbow includes buckle or greenstick fracture of the distal humerus, growth plate injury of the distal humerus or proximal radius. A history of a pulling injury makes a fracture unlikely. Radiographs may be necessary to rule out a fracture if the history is not consistent with a pulling injury or a fracture is suspected for other reasons. Treatment involves a reduction procedure. Various reduction procedures have been described. The most common procedure is the supination of the forearm (usually with the elbow in flexion, but it can also be done in other ways). Hyperpronation of the forearm with the upper extremity held up high has also been described. A click may be palpated at the level of the radial head suggesting successful reduction (5). The response to reduction of the displaced ligament is diagnostic. The child starts using the arm again, and there is usually no residual tenderness (4). The elbow may be immobilized in a sling for a day (usually not necessary), and if needed, acetaminophen can be given for pain (5). Parents are advised that this injury may recur up to age 5 or 6 years, but it does not signify any elbow problems in later life. It is prudent to minimize the risk of a pulling injury.

Knee problems are a common musculoskeletal presentation in primary care. The anatomy of the knee joint is very complex. Detailed description of all of its structures goes beyond the scope of this chapter. It is important to discuss some of the anatomical features of the knee that are more commonly injured. The tibiofemoral joint is a combination of a hinge, a sliding, and a gliding joint. There are several ligaments at this joint which are susceptible to injury. The medial collateral ligament (MCL) resists valgus angulation of the knee. The lateral collateral ligament (LCL) resists varus angulation. The anterior cruciate ligament (ACL) resists anterior displacement of the tibia on the femur. These ligaments are commonly injured. The menisci of the joint act to deepen the articular surfaces for load transmission, reduce stresses on joint surfaces, and act as a secondary stabilizer to enhance joint stability. These structures are also susceptible to injury. (8)

Patient history is a key element in evaluating the knee. Onset, type, quality, location, and duration of pain or other symptoms; (alleviating and aggravating factors), attempts to remedy the problem and any associated symptoms help to make the diagnosis (7). The mechanism of injury is a key factor in evaluating knee injury. Pivoting injury with a "pop" and swelling suggest an ACL injury. Twisting injury with a history of knee locking may indicate a meniscal tear. Varus or valgus forces point to the probability of LCL or MCL injury respectively. Physical examination of the knee includes observation, palpation of the soft tissues and bony anatomy, and range of motion of the affected knee in comparison to the unaffected knee. Specific testing of the knee for laxity of ligaments are helpful in making the diagnosis of knee injury. Some examples of these tests include the anterior drawer test to determine ACL laxity, and the valgus and varus stress tests to determine MCL and LCL laxity (8). McMurray's test and Apley's grind test are used to assess possible meniscal injury (4). It is important to remember that injury to one of the ligaments or menisci of the knee may be associated with other concomitant injuries to the knee. Therefore, it is important to examine the patient for those possibilities. Imaging procedures to evaluate knee injury include anteroposterior and lateral plain radiographs to rule out fractures. MRI may be appropriate to rule in possible ligamentous or meniscal injuries. Treatment depends on the type and severity of injury, which may include hinged bracing, analgesics for pain, surgical treatment and pursuant physical therapy. Most medial collateral ligament injuries may heal without surgery. Patient education on preventative measures such as proper conditioning prior to athletic activity is helpful (4).

Shoulder injuries in young athletes can be of various types. Acute dislocation and acute subluxation of the glenohumeral joint, chronic subluxation, impingement syndromes, rotator cuff injuries and acromioclavicular injuries are common injuries of the young athlete (6). Anterior dislocations comprise 85-95% of all shoulder dislocations and can occur in dominant and nondominant extremities (6). Patients often present holding the arm in slight abduction and internal rotation and report pain upon attempting to rotate the arm. A mass (the humeral head) may be palpable over the anterior shoulder (deltopectoral groove). The patient may also report "dead arm" syndrome; transient loss of sensation, numbness and tingling of the involved extremity. Axillary nerve injury may occur in this type of injury and presents by loss of sensation over the lateral deltoid as well as decreased strength of the deltoid.

A thorough history and physical examination are key to identification of shoulder instability. In patients with an acute injury, pertinent historical information include arm dominance, previous episodes of injury, and neurologic symptoms. Position of the extremity and direction of the force when the injury occurred are also important. Examination should include assessment of the neurovascular system, palpation of the musculature and the bony anatomy. Rotator cuff strength and range of motion, as well as documentation of external rotation are important findings that suggest acute dislocation. Standard radiologic studies of the shoulder include: anteroposterior views with shoulder in internal and external rotation, an axillary or modified axillary view and the Stryker notch view (6).

X-ray confirmation of a shoulder dislocation is preferable before a reduction procedure is attempted. It should be noted that fractures of the humerus are more common in children, while shoulder dislocations are more common in older teenagers. Acute dislocation requires prompt reduction. There are several common reduction methods. The Stimson technique utilizes a weight which is taped to the forearm. The patient lies prone with the weighted upper extremity hanging over the side of an elevated gurney. Reduction occurs gradually. The external rotation method is probably the easiest method, requiring the least assistance and equipment. With the patient lying supine or sitting upright, the procedure starts with the elbow flexed at 90 degrees with the forearm in a position of comfort and the humerus and elbow held adducted against the side of the chest. The humerus is slowly externally rotated using the forearm as a lever, keeping the elbow against the body. With gradual external rotation, reduction occurs spontaneously as the forearm begins to point away from the body in the coronal plane (i.e., extreme external rotation) (9). Following reduction, the arm should be immobilized for three weeks in a shoulder immobilizer (a sling with an additional strap to hold the forearm against the torso). In patients under age 25 years, many orthopedic surgeons believe surgical repair should be a consideration to prevent further episodes of anterior dislocation and arthritic changes. Rehabilitation of the injured shoulder involves exercises and close follow-up with a physical therapist or athletic trainer (6).

Questions

1. What is the usual mechanism of injury in an ankle sprain?
2. Which ankle ligament is most commonly injured?
3. Early management of acute ankle sprain employs RICE. What does this mnemonic stand for?
4. What is the mechanism of injury in nursemaid's elbow?
5. How do you reduce subluxation of the radial head (nursemaid's elbow)?
6. If you suspect an ACL knee injury in a patient, what specific test can you do to assess ACL laxity. Should you be worried about other injuries in this patient?
7. What nerve is commonly injured in an anterior dislocation of the shoulder. What are the typical neurologic deficits associated with this injury?
8. Describe two procedures to reduce an anterior shoulder dislocation.

Related x-rays

Ankle sprain: Inaba AS. Ankle Injuries: A Sprained Ankle ? In: Yamamoto LG, Inaba AS, DiMauro R. Radiology Cases In Pediatric Emergency Medicine, 1995, volume 3, case 3. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v3c03.html

Series of ankle x-rays: Inaba AS, Yamamoto LG. Test Your Skill In Reading Pediatric Ankles. In: Yamamoto LG, Inaba AS, DiMauro R. Radiology Cases In Pediatric Emergency Medicine, 1995, volume 3, case 5. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v3c05.html

Shoulder dislocation: Yamamoto LG. Closed Reduction of a Dislocated Shoulder. In: Yamamoto LG, Inaba AS, DiMauro R. Radiology Cases In Pediatric Emergency Medicine, 1996, volume 4, case 12. Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v4c12.html

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Answers to questions

1. Combination of plantar flexion and inversion.
2. Anterior talofibular ligament.
3. Rest, Ice, Compression, Elevation.
4. Traction injury resulting from being lifted or pulled by the hand or arm.
5. Supination or hyperpronation of the forearm at the elbow.
6. Anterior drawer test assesses ACL laxity. Physician should assess for other structural abnormalities in the affected knee, as multiple ligaments and/or menisci may be injured.
7. Axillary nerve injury. Injury to the axillary nerve can result in transient loss of sensation, tingling and numbness to the lateral aspect of the deltoid.
8. Stimson technique or external rotation method. See text.

Chapter XIX.8. Sports Injuries
Brent K. Ogawa, MD

Osgood-Schlatter Disease

This is a 12 year old male soccer player who comes into the office with a chief complaint of pain to both knees. He reports a gradual onset of knee pain in the front of both of his knees that started about one year ago. The pain seems to be in the same spots and is worse after a hard practice or game and with running up and down hills. He noticed a "bump" on both of his knees recently that is tender if he falls or accidentally bangs them. The patient does not remember an initial history of trauma or injury. He is otherwise healthy with normal birth and development.

Examination is unremarkable with the exception of his knees. He is comfortable, in no significant acute pain. His right and left knee findings are identical. A mild prominence over the tibial tuberosity is visible. No erythema, edema or effusions are noted. No patellar grind is noted. The patella is normally placed and there is no tenderness over the patella. He has localized tenderness over the tibial tuberosity. His knee range of motion is good, but he experiences pain over the tibial tuberosity when he is asked to extend his knee against force (such as against gravity, or against resistance from the examiner). Motor strength is good. Varus and valgus stress tests are negative. McMurray, anterior drawer, Lachman, and posterior drawer tests are all negative.

Radiographs demonstrate moderate prominence of the tibial tuberosities bilaterally. There is mild soft tissue swelling. No evidence of fracture.

He is instructed to rest and apply ice massages to the area, focus on stretching his hamstrings, and to take acetaminophen. He is permitted to ambulate normally and jog briefly, but he must stop if any pain occurs. After 5 weeks, the pain subsides and after about one year, he is symptom free. There remains mild, nontender prominences over both knees as he becomes older.

Traction apophysitis of the tibial tuberosity was first described independently by both Osgood and Schlatter in 1903 (1). This disease is usually seen in adolescents or older children 11-15 years of age, with a male to female predominance of 3:2 (2). Girls present earlier because the secondary ossification center of the tibial tuberosity appears 2 years earlier. Osgood-Schlatter is seen in children/teens who are very active in sports requiring strenuous quadriceps muscles such as basketball and volleyball. Jumping puts the most force on the quadriceps and the insertion of the patella tendon into the tibial tuberosity. Osgood-Schlatter is also common in running sports such as soccer, baseball and football, but less so than with the jumping sports. This disease is seen more often on the left side and 25% of patients have a bilateral appearance.

The exact etiology remains controversial, although repetitive trauma is the most widely accepted theory. Other less likely theories include avascular necrosis of the tibial tuberosity (although blood supply is abundant), infection (although patients are afebrile and without leukocytosis), and degeneration of the patella with heterotopic ossification (although histological studies show no tendon necrosis and normal tendon insertion) (2,3).

Growth of the proximal tibia is unique because it involves two growth centers in close proximity: the proximal tibial physis and the tibial tuberosity apophysis. An apophysis is a growth plate, which does not contribute to the length of the bone. It is common for a tendon to insert over an apophysis, such as in the tibial tuberosity (patella tendon), calcaneus (Achilles tendon), etc. The cartilage growth plate of the apophysis is a weak spot which is susceptible to microseparation with trauma or overuse (pulling, traction). Anatomy of the tibial tuberosity starts at 12-15 weeks of fetal growth; however, there isn't a recognizable tibial tuberosity growth plate until after birth. Southwick and Ogden described the development of the tibial tuberosity in 7 stages; 3 prenatal and 4 postnatal. Stages 1-3 involve fibrovascular ingrowth and vascularization of the area with anterior outgrowth. Postnatal stages include a separate and distinct tibial tuberosity growth plate (stage 4) that later joins with the tibial growth plate (stage 7). There is a distinct secondary ossification center in the distal portion of the tuberosity (stage 5). During maturation (stage 6) there is a coalescence of the proximal tibial epiphyseal ossification center with the tuberosity ossification center. In the final stage (stage 7), there is fusion to form a contiguous structure. The vascular anatomy of the tuberosity is plentiful even until age 10-12. Therefore, because of its unique anatomy and vascular supply, combined with excessive pulling forces of the extensor mechanism, there is a failure of the secondary ossification center, ultimately leading to the disease.

The pain is localized to the anterior aspect of the proximal tibia over the tibial tuberosity. There is a local prominence and tenderness on exam. Although patients may complain of pain with full extension of the knee (especially against force), they have full range of motion. They may describe a dull ache exacerbated by jumping or stair climbing. Walking on flat surfaces does not cause pain. Patients may often have symptoms for 6-12 months prior to seeking medical attention. Although the tibial prominence may be highly indicative of Osgood-Schlatter in many cases, a full knee exam should be performed to rule out other intra-articular pathology.

Unless other pathology is suspected, radiographs of the knee are usually unnecessary, since this is largely a clinical diagnosis. In more severe cases, lateral radiographs of the knee will often show a decrease in homogeneity of the infrapatellar fat pad, soft tissue swelling, and a prominence/fragmentation of the tibial tuberosity.

The differential diagnosis includes acute stress fracture, contusion of the tibial tuberosity, prepatellar bursitis, and patellar tendonitis. Some have termed Osgood-Schlatter as a "tendonitis" of the patellar tendon insertion. Some consider the two terms, tendonitis and apophysitis to often be interchangeable. Other pathology may also be considered including osteomyelitis or tumor.

Despite the ominous sounding name, the end result is often the same with or without treatment; therefore, alleviating parental fear is important (2). Treatment is mainly symptomatic and involves reducing forceful use of the quadriceps, which equates to playing less, resting more during games and practices, and less jumping. Hamstring stretching, ice, and NSAIDs may be useful as needed. Corticosteroids are not used because subcutaneous atrophy and fat pad necrosis may occur. If the pain is severe, a knee immobilizer may be used to allow for both decreased tension over the patellar tendon by limiting extension. A cylinder cast was used in the past; however, a knee immobilizer is better because it allows for removal to prevent atrophy and stiffness, and allows the patient to shower. Surgery is rarely indicated. Being skeletally immature, these patients are at risk for subluxation of the patella, patella alta (high riding patella), nonunion of the bony fragment of the tibia, and premature fusion of the anterior part of the epiphysis leading to genu recurvatum (hyperextension of the knee). If patients remain symptomatic, surgery may be performed (rarely), usually after reaching skeletal maturity.

After acute symptoms resolve, gradual strengthening exercises of the extensor mechanism using isometric or short-arc terminal extension techniques should be performed. The use of knee pads to prevent reaggravation of contusions should be stressed to both patients and parents.

The prognosis for this disease is good with spontaneous healing usually occurring. As the disorganized ossification fuses with the beaklike portion of the epiphysis, symptoms diminish (4). Often patients decrease their activity voluntarily secondary to pain. Although the symptoms may decrease with activity reduction, local tenderness may persist. In the adult, a local prominence of the tibial tuberosity may remain; however, this is usually painless.

Sever's Disease

This is a 13 year old boy who presents to the office with a chief complaint of right heel pain. The patient states he has gradually noticed this pain since the beginning of basketball season 2 weeks ago. The pain is a dull, 5/10 ache over his right heel that is worse with running, especially when running on the hardwood floor. He has tried ice, which provides only temporary relief until the next practice. He is not taking any pain medications. There is no history of trauma or known injury and he is otherwise healthy. Birth and developmental history are unremarkable.

Examination is unremarkable except for his right lower extremity. He is comfortable in no acute pain. There is no visible deformity, muscle atrophy, or erythema. There is minimal soft tissue swelling and moderate tenderness to palpation over the back of the right calcaneus. Ankle range of motion is normal. He ambulates normally and he is even able to jump up and down.

Radiographs of his right heel are obtained, which demonstrate no specific abnormality. He does have an open growth plate (apophysis) over the Achilles tendon insertion region, but this is noted to be normal for his chronologic and bone age.

He is diagnosed with Sever's disease. He is instructed to rest from athletic activity for 4 weeks, but he is permitted to ambulate normally. He is also instructed to apply ice and take NSAIDs if the pain continues. A heel wedge is placed in his right shoe, which he later reports helps to alleviate the pain. After 4 weeks, he focusses on stretching and strengthening exercises for his calves and hamstrings. He subsequently recovers and returns to his normal athletic function.

Sever's disease (calcaneal apophysitis), first described in 1912 by JW Sever, is inflammation of the open calcaneal growth plate (Achilles tendon insertion) secondary to traction on the apophysis of the os calcis by the Achilles tendon (5). This disease is commonly seen in children 8-13 years old and is more prevalent in runners, especially soccer and basketball players who play on hard or artificial surfaces, or football/baseball players who play with cleats which permit them to gain excess traction into the ground. The mechanics of this injury are similar to Osgood-Schlatter disease except that the major stress is running and pushing forward in Sever's, compared to jumping in Osgood-Schlatter's. Tension is placed on the calcaneus by the strong shearing forces caused by the plantar fascia and triceps surae. Associated pathology thought to predispose to this disease includes internal tibial torsion, forefoot varus, and tight heel cords (6,7).

Clinically these patients present with heel pain over the posterior calcaneus near the Achilles tendon insertion. Soft tissue swelling and induration may be present, although less often. They may have an antalgic gait secondary to pain, but in most instances, their gait is normal during medical evaluation. Most of their pain and discomfort is sustained during athletic activity when stress on the Achilles tendon insertion is maximal. After a period of rest, symptoms commonly subside. Radiographs are not necessary, but if done, three views should be included: AP, lateral, axial (Harris views). Radiographs may show a sclerotic and fragmented calcaneal apophysis in severe cases, but most often, radiographs are normal. An open growth plate is present in Sever's patients, and symptoms usually subside as the growth plate achieves fusion/closure. Oblique views and CT may be necessary to identify occult fractures. Bone scanning may be useful to rule out a stress fracture (8).

The differential includes stress fracture, avulsion fracture of the calcaneus, Brodie's abscess, simple bone cyst, plantar fasciitis, or Achilles tendon rupture.

Treatment for this disease is mainly symptomatic. This includes rest from activity, ice, and NSAIDs as needed. Most patients with mild Sever's disease can still play, but they should be told to rest when pain occurs. A posterior heel wedge 0.5 to 1.0 cm in height is recommended. By raising only the heel, tension is reduced on the Achilles tendon insertion site on the calcaneus. Shock absorbing insoles may also be used. Once acute symptoms have resolved, patients should begin stretching and strengthening exercises of the hamstring and calf muscles. Athletic activity can be gradually resumed. The exact time frame for resolution of symptoms varies. If conservative measurements fail after 6-8 weeks, a bone scan or other studies to seek more occult sources of pain should be considered.

Little League Elbow

This is a 13 year old right handed boy who presents to the clinic with a chief complaint of right elbow pain. The patient has noticed a gradual onset of pain over the past two months since baseball season started. He is the star pitcher for his little league team and pitches full games twice per week. He also practices a lot during the week. He has complained of pain during practices, but has been told to continue practicing; "no pain, no gain." The pain is most severe over the medial aspect of his right elbow and does not radiate. He is able to do normal activities of daily living. His wrist and shoulder are unremarkable. His parents are concerned about him missing the All-Star game if he doesn't continue to perform at a high level.

Exam: His is exam is normal with the exception of his right elbow. No visible deformity, edema, or erythema. He is tender to palpation over the medial epicondyle. An elbow contracture of 15 degrees to full flexion is noted. He has full ROM about the shoulder and wrist. Sensation is intact. Upper extremity strength is good and sensation is intact. Perfusion, pulses and reflexes are all normal. Radiographs of his right elbow are obtained and show a minimally displaced right medial epicondyle fracture.

Despite initial apprehension, the patient and his parents decide to cease activity. Because there is minimally displacement (<2mm), a posterior splint is applied for 2 weeks. On return to the clinic, the patient reports improvement of his symptoms. The splint is removed and active range of motion exercises are taught. The patient continues these diligently. Six weeks later, after radiographic evidence of union, the patient is allowed to start a specific throwing program. He is back to pitch in the championships the following season. The league commissioner decides that each team must keep an accurate pitching record of the number of pitches thrown per game. The community sports medicine physician is also asked to educate coaches and parents about the importance of identifying little league elbow early.

The term "Little League elbow" is used to describe a group of pathologic entities in and around the elbow joint in young throwers. The mechanism includes pitching, tennis serving, volleyball spiking/serving, football and javelin throwing. The syndrome is a result of a repetitive valgus stress during overhead throwing. This valgus stress results in lateral compression and medial traction on the elbow. The injury has expanded to include (9): 1) Medial epicondylar fragmentation and avulsion. 2) Delayed or accelerated apophyseal growth of the medial epicondyle. 3) Delayed closure of the medial epicondylar growth plate. 4) Osteochondrosis and osteochondritis of the

capitellum. 5) Deformation and osteochondritis of the radial head. 6) Hypertrophy of the ulna. 7) Olecranon apophysitis with or without delayed closure of the olecranon apophysis.

The biomechanics of throwing are complex. The physical stresses associated with throwing produce exceptional forces in and about the elbow in the throwing athlete of any age. These forces include tension, compression, and shear localized to the medial, lateral, and posterior aspects of the elbow (10).

1. Tension overload of the medial elbow restraints: early and late cocking phases.
2. Compression overload on the lateral articular surface: early and late cocking phases.
3. Posterior medial shear forces on the posterior articular surface: late cocking and follow through phases.
4. Extension overload on the lateral restraints: acceleration phase.

A comprehensive history is important and should include age, handedness, activity level, sport played, and history of trauma. The age of the thrower can be helpful in the differential and is divided into three groups: 1) childhood (terminates with appearance of all secondary centers of ossification), 2) adolescence (terminates with fusion of all secondary centers of ossification to their respective long bones), and 3) young adulthood (terminates with completion of all bone growth and achievement of final muscular development) (9).

During childhood, pain to the medial epicondyle secondary to microinjuries at the apophysis and ossification center is common. In adolescence, muscle strength, muscle mass, and throwing forces increase. Valgus stress of the elbow results in an avulsion fracture of the entire medial epicondyle. Some athletes develop enough chronic stresses to cause delayed union/malunion of the medial epicondyle. By young adulthood, the medial epicondyle is fused and injuries tend to occur to muscular attachments and ligaments. The flexor muscles and ulnar collateral ligaments are often injured.

Examination should include both elbows looking for atrophy/hypertrophy, ROM, bony deformity, flexion contractures, and carrying angle. Also neurological and vascular exams with attention to the ulnar nerve should be performed.

Radiographs (AP, lateral, oblique) and comparison views are essential. Common findings include an immature elbow with elbow enlargement, fragmentation, and beaking or avulsion of the medial epicondyle. Lateral lesions usually involve the subchondral bone and manifest as osteochondrosis or osteochondritis dissecans (OCD) of the capitellum or radial head. Posterior lesions present with hypertrophy of the ulna causing chronic impingements of the olecranon tip into the olecranon fossa. CT and MRI are also useful modalities.

The American Academy of Pediatrics and youth baseball organizations have made recommendations to reduce the risk of overuse elbow injuries in young athletes by providing leagues and coaches with guidelines limiting the number of pitches per day or per game, a young athlete can throw. It is far preferable to prevent these injuries, than it is to recover from these injuries. The onset of pain or swelling suggests the earliest onset of an injury. Playing through such pain worsens the injury, so this practice should be discouraged. A basic strategy to reduce the risk of these injuries is to restrict further elbow throwing stress for the remainder of the day once the onset of pain occurs.

Medial tension overload injuries are the most common and usually resolve within 4-6 weeks of rest, ice, and NSAIDs. After symptoms resolve, gradual return to throwing is allowed. If disability continues for an extended period of time, throwing should be disallowed until the next season.

Medial epicondylar fractures occur with substantially more acute valgus stresses applied through violent muscle contraction causing an avulsion fracture of the medial epicondyle. This causes a painful elbow with tenderness over the medial epicondyle and elbow flexion contracture that may exceed 15 degrees. In minimally displaced (<2mm) or non-displaced fractures, a single posterior splint for 1-2 weeks then progression to active ROM exercises is commonly used. When radiographic evidence of union is noted, a specific progressive throwing program is started. In moderately displaced fractures (>2mm) open reduction with internal fixation hardware is performed with early ROM exercises at 1-2 weeks to regain flexion and extension.

Medial ligament rupture to the ulnar collateral ligament is not common in young athletes and is seen more in adults. Patients may have medial tenderness for months to years before the ligament is injured, usually in a sudden catastrophic event. If the patient desires to continue throwing, surgical repair is needed. If the injury is detected early, conservative treatment including rest and alternating heat/ice is recommended.

Lateral compression injuries, such as Panner's disease (osteochondrosis), is a malady of the growth degeneration or necrosis of the capitellum and is followed by regeneration and recalcification. Panner's is a focal, localized lesion of the subchondral capitellum and its articular cartilage. It is a self-limiting condition where the capitellum epiphysis essentially assumes a normal appearance as growth progresses. Panner's usually affects a younger population and onset is acute with fragmentation of the entire capitellar ossific nucleus. There are no loose bodies and no late sequelae unlike osteochondritis dissecans. These patients are also younger. Initial treatment of Panner's includes rest, avoidance of throwing, and sometimes a posterior splint until acute symptoms resolve. Radiographic follow up is essential to ensure adequate healing. Late deformity and collapse of the articular surface of the capitellum are rare.

Osteochondritis dissecans (OCD) is a focal lesion of the capitellum occurring in 13-16 year olds. They present with elbow pain and a flexion contracture of greater than or equal to 15 degrees. OCD of the capitellum is secondary to the compressive forces occurring between the radial head and capitellum during throwing. Again, these patients are older than Panner's disease. The etiology of OCD in the elbow is unclear. Theories include ischemia, trauma, and genetic factors. These patients present with poorly localized, dull pain with decreased range of motion during extension with "locking and catching," also unlike Panner's disease. CT and arthroscopy are beneficial in determining the extent and size of the lesion. OCD lesions can be divided into three types: Type I) Intact with no displacement or fracture of the articular cartilage. Treatment includes rest, splinting 3-4 weeks if the pain is severe, followed by ROM exercises. Type II) Shows evidence of fracture or fissure of the articular cartilage. Determining the size and stability of the fragment is important. If the fragment is small, arthroscopic removal may be performed. If the fragment is large, arthroscopic pinning is necessary. Type III) Complete detachment with the fragment lying freely. Treatment includes either trying to reattach the loose fragment or removal. Pain may be relieved; however, there may be little improvement in ROM. These patients should be seriously counseled about the dangers of continued throwing and are urged to abstain.

Posterior extension and shear injuries are uncommon in young throwers but the incidence increases with age. These types of injuries can be divided by age. 1) Childhood: Osteochondrosis of the olecranon. Treatment includes rest and gentle ROM exercises. Flexibility and strengthening are initiated once acute symptoms subside. 2) Adolescents: Avulsion fragments and lack of apophyseal fusion. For avulsion fragments, treatment usually requires arthroscopic removal. If there is lack of apophyseal fusion, rest and immobilization can produce good results. 3) Young adults: Partial avulsion of the olecranon and osteophyte formation at the tip of the

medial border of the olecranon. Partial avulsion of the olecranon requires surgical reattachment of the olecranon and triceps. Osteophytes should be removed to decrease pain and increase ROM.

In summary, overuse injuries to the elbow of young throwing athletes occur often. They can be seen not just in baseball pitchers but also in quarterbacks, tennis players, volleyball players and javelin throwers. Because the biomechanics of throwing are complex, the physical stresses can cause a group of pathologic entities to include the medial, lateral, and posterior aspects of the elbow. Preventing these types of injuries involves teaching proper throwing mechanics, keeping an accurate pitching count, predetermining a stopping point based on number of pitches thrown, and recognizing early warning signs and stopping once the pain starts. Although many of these injuries have been blamed on throwing curve balls, some studies have shown that a properly thrown curve ball causes no more injuries than the traditional fastball (11,12,13).

Orbital fracture/Hyphema

This is a 10 year old boy who presents to the ED with a chief complaint of a "black eye". He was playing in a roller hockey game when a hockey stick was swung high and struck him in the face. Although he was wearing a helmet, he was not wearing protective eyewear. He complains of severe eye pain and tenderness around his right eye. He states he is able to see out of his left eye, but not his right eye. There was no loss of consciousness or other associated injuries. He is able to walk in to the ED with his parents.

Exam: He is alert and cooperative in moderate discomfort. He has his right eye closed during most of the examination. A large area of ecchymosis is noted over the right periorbital region. The skin is intact with no active bleeding. He has severe tenderness over the inferior orbital region. There is moderate soft tissue swelling of the eyelids. He opens his eye with difficulty and apprehension. It is still difficult to see his eye because of the periorbital swelling. A small amount of blood is visible in the anterior chamber. He is able to sense light from the right eye, but his vision is blurry. Visual acuity is 20/50 in the right eye and 20/20 in the left eye. His EOMs are probably conjugate, but it is difficult to be certain because of the periorbital swelling. He does complain of some eye pain with EOM. Pupils are equal and reactive to light. Normal sensation to light touch over his right cheek is noted. Fluorescein examination shows no evidence of corneal abrasion. His left eye exam is unremarkable. The remainder of his face and head are without signs of injury.

It is decided not to order any plain film radiographs. A CT scan of the head with special views of the orbit is ordered, which shows a normal brain and skull. Coronal CT cuts show a fracture of the floor of the orbit with no muscle entrapment.

He is diagnosed with an orbital floor fracture and hyphema. Ophthalmology is consulted and further evaluation for the hyphema includes an intraocular pressure measurement, which is found to be normal. The patient and parents are told to limit his activity for the first 72 hours without television or video games. His immunization records are current and the patient is sent home with a narcotic analgesic and follow-up in 3 days. He recovers well with no diplopia or glaucoma complications. The next season, he is sporting a new pair of safety goggles to every game and practice. The community league also implements a new rule requiring protective eyewear.

Orbital injuries are common injuries in athletes, especially those in high-risk sports with high-speed objects such as sticks, bats, balls, pucks, or aggressive body contact. Eye injuries can almost always be prevented with protective eyewear. Males are at higher risk for orbital fractures because of their increased incidence of trauma.

The aperture of the bony architecture surrounding the eye does not allow an object with a radius of greater than 5 cm to penetrate the globe (14). Fractures of the inferior rim are the most common. The thin orbital floor (maxilla) and the medial wall (ethmoid) are the weakest portions of the orbit. Internal wall fractures with or without bony rim fractures can occur. A direct blow to the bony rim may not cause a bony rim fracture, but can be enough to increase intraorbital pressures (as the globe is compressed) resulting in a "blowout fracture" of the weakest point of the orbital wall, which is usually the floor of the orbit.

Anatomically the orbit consists of 6 facial bones (14,15):

1. Frontal bone: superior orbital ridge and upper medial orbital ridge
2. Zygoma: lateral orbital rim
3. Maxilla: inferior and lower medial rims
4. Lacrimal: medial rim separating orbital from nares
5. Ethmoid: medial wall and part of posterior wall
6. Sphenoid: posterior orbit

Related anatomical structures that can be injured during an orbital fracture include the optic nerve, periorbital fat, extraocular muscles, and the inferior orbital nerve.

The principle morbidity associated with orbital fractures is eye injury. These injuries are multiple and can include corneal abrasion, lens dislocation, iris disruption, choroid tear, scleral tear, ciliary body tear, retinal detachment, hyphema, ocular muscle entrapment, and globe rupture. The patient should be questioned regarding epistaxis or clear fluid from nares or ears, loss of consciousness, visual problems, hearing problems, malocclusion, and facial numbness or tingling. Other specific questions regarding the eye include the presence of diplopia, painful eye motion (entrapment or periorbital edema), photophobia, flashes of light (retinal detachment), or blurred vision (hyphema, vitreous hemorrhage, retinal detachment) (14,16,17).

When an injury near the eye occurs, a thorough exam should be performed. This includes visual acuity, inspection for abrasions, laceration, foreign bodies, changes in pupillary dimension or reactivity to light. Any change in visual acuity, blood in the anterior chamber, or change in the shape of the iris should warrant a consult with an ophthalmologist. The patient should also be inspected for asymmetry (proptosis or enophthalmos), corneal abrasions (fluorescein), nasal septum swelling/deviation, or clear rhinorrhea, which might be CSF. They should have their supraorbital ridge and frontal bone palpated for step-off fractures, and their hard palate and teeth palpated for stability. Evaluate the supraorbital, infraorbital, inferior alveolar, and mental nerve distributions for anesthesia.

These patients may present with ecchymoses, enophthalmos of the globe (sunken eye), vertical dystopia (a change in vertical position of the pupil in relation to the unaffected side), or numbness in the area on the ipsilateral cheek supplied by the infraorbital nerve. Although a "black eye" was once felt to be a relatively benign injury for which medical attention was often not sought, many instances of periorbital ecchymoses are due to orbit fractures.

Radiographically, routine facial views include Waters, Caldwell, and lateral projections (14,15,16). The Waters view is used for identifying inferior orbital rims, nasoethmoidal bones, and maxillary sinuses. The Caldwell projection provides the best view of the lateral rim and ethmoid bone. Lateral views may show air-fluid levels in the posterior maxillary sinus if the patient is lying supine. C-spine films are indicated if the patient complains of neck pain or if a suspected cervical injury cannot be ruled out.

Plain film radiographs have been largely replaced by CT scans. A CT scan with coronal views (done by tilting the patient's head in the CT ring, or angling the CT ring) is the most useful for evaluating inferior and medial walls of the orbit to diagnose a blowout fracture. In patients without ocular injury or entrapment, a CT scan is not necessary, however it is still more useful and diagnostically superior to plain film radiographs. CT may be helpful in identifying direct optic nerve involvement and the presence of retroocular edema or hematoma compressing the nerve.

A forced duction test can determine if limitation of ocular movements is due to entrapped soft tissues or to edema or contusion of a motor nerve or muscle. This is performed by anesthetizing the affected eye with topical anesthesia, grasping the sclera with a fine toothed forceps at the level of the inferior rectus muscle and moving the eye in a superior/inferior direction. If the globe moves easily, entrapment is unlikely (14). In clinical practice, this test is only rarely performed, since it is more convenient to merely wait to see if diplopia subsides with time. If the EOM function normalizes, then the EOM dysfunction is non-surgical (i.e., probably due to edema), while persistence of EOM dysfunction indicates the presence of muscle entrapment requiring surgical release.

Depending on the extent of injury, consultation with ophthalmology, ENT, oromaxillofacial surgery, or plastic surgery may be warranted. Acetaminophen or narcotic analgesics can be used for pain. NSAIDs are sometimes used, but these may cause bleeding, so it is preferable to avoid these especially if a hyphema is present. Tetanus prophylaxis may be indicated. Blowout fractures without associated injuries do not require hospitalization. Even patients with signs of entrapment may be discharged home because most entrapment resolves as the swelling goes down. They should; however, return if there is a change in visual acuity, increased pain, or flashing lights. If entrapment continues for 2 weeks, surgical intervention may be needed.

A hyphema is a collection of red blood cells in the anterior chamber of the eye. In the United States the incidence of hyphema occurs in 20/100,000 per year. Hyphema occurs more often in males (3:1) and is usually seen in a younger population, less than 30 years old (18). Trauma is the most common cause of hyphema, often seen in baseball or hockey athletes where a blunt compressive force hits the globe causing tears in the ciliary body, iris, and other structures in the anterior segment. Other non-sports related causes of hyphema include microvascular disease such as diabetes causing neovascularization, retinal ischemia, carotid stenosis, or iatrogenic (post-intraocular surgery), sickle cell disease, pupillary microhemangiomas, iritis, or intraocular tumors.

Hyphemas can be divided into microhyphema (RBCs detectable by microscopy only) or macrohyphema (visible even without the aid of a slit lamp). Corneal bloodstaining results from blood being forced into corneal endothelial cells. It is an ominous sign and signifies the need for surgical evacuation of the hyphema. Intraocular pressure increases secondary to RBCs and their blood products clogging the trabecular outflow meshwork. Secondary angle-closure glaucoma resulting from pupillary block can occur. This occurs when the clot completely occludes the pupil/lens interface, blocking the flow of aqueous from the posterior to anterior chamber. People of African or Mediterranean descent are prone to sickle cell hemoglobinopathy and thus have a higher incidence of developing glaucoma due to the rigidity of RBCs causing slower passage through the trabecular meshwork and elevated intraocular pressure (18).

Historical data important to illicit include the mechanism of injury, type of assaulting object, whether protective eye wear was used, ethnic origin, and past ocular history. The ocular examination should be certain to rule out a coexisting ruptured globe. Visual acuity, pupillary reaction, extraocular movement, signs of corneal staining, and intraocular pressure are also important aspects of the examination. An exophthalmometer can be used to look for exophthalmos related to ocular trauma.

Treatment includes both operative and nonoperative measures. In patients without an increase in intraocular pressure, behavioral modifications begin with limiting activities such as reading, which cause rapid shifts in the globe. Within the first 72 hours, rebleed is most common, therefore, this is the crucial time when children may have to be bedrested. It is especially important to limit activities in infants and children who watch television or play video games. Watching television from a distance greater than 10 feet limits the amount of extraocular movement. In hyperactive children, bilateral patching may be required to minimize activity level. Patching of the affected eye only, is not beneficial because movement of the contralateral eye will cause movement of the affected eye (18). In general, patients should keep activity to a minimum for at least the first 5 days to prevent a rebleed.

Patients with concurrent elevation in intraocular pressure (IOP) may require both topical and oral ocular hypotensive medications. Persistent elevated IOP can cause optic nerve damage. Topical beta blockers decrease aqueous production and IOP. Osmotic diuretics decrease IOP by reducing vitreous volume. In general, patients with an IOP higher than 30mm Hg (or 24mm Hg in sickle cell patients) should receive IOP lowering medication. Cycloplegics and topical steroids, which treat associated iritis may also be used. Cycloplegics are anticholinergic agents that block the response of the iris sphincter muscle and ciliary body to cholinergic stimulation, causing paralysis of accommodation (cycloplegia) and pupillary dilation (mydriasis). Antifibrinolytics such as aminocaproic acid may be used to prevent recurrent hyphemas, but this medication may cause serious adverse effects. Carbonic anhydrase inhibitors decrease aqueous production and IOP.

Supportive treatment including wearing a metal shield or glasses is recommended. Head elevation keeps the central cornea and pupillary aperture free of blood. Patients should also avoid aspirin to prevent further bleeding.

The most severe complication is a rebleed (usually seen in the first 72 hours). Hyphema resulting from a rebleed is usually more extensive than the initial trauma. Rebleeding may present as a total hyphema with blood filling the entire anterior chamber. This is called an "8-ball" hyphema (18). Such a significant hemorrhage leads to elevated IOPs and corneal blood staining. Hemosiderin collects in the stroma causing a yellow appearance in the cornea. This usually resolves spontaneously in a few years. Glaucoma may lead to optic nerve atrophy. This is especially seen in sickle cell patients.

Prognosis depends on the size of the hyphema. Patients with a small-sized hyphema can be treated with simple management and have a good prognosis. Total hyphema is difficult to treat and visual outcome is poor. Promoting public awareness in parents regarding eye safety for their children is important but often difficult, especially in adolescents when image is important. Just as wearing a helmet in football is mandatory, wearing goggles in high-risk sports should become obligatory.

Prevention of orbital and ophthalmic injuries includes wearing safety glasses or goggles in those who participate in high-risk sports in which balls, bats, or pucks are used.

Questions

1. What is the definition of Osgood-Schlatter's disease?
2. Who is Osgood Schlatter disease and Sever's disease commonly seen in?
3. Is it common to have Osgood-Schlatter disease in both knees?
4. What is the definition of Little League elbow?
5. What types of athletes are subject to Little League elbow besides baseball pitchers?
6. What is a blowout fracture of the orbit?

7. What is the best imaging technique to identify a blowout fracture?
8. How can you reduce elevated intraocular pressure?
9. What is the most severe complication of a hyphema and how can you prevent this?

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Answers to questions

1. Traction apophysitis of the tibial tuberosity.
2. Osgood-Schlatter: Usually older children or adolescents with male: female of 3:2. Those who do forceful contraction of the quadriceps (jumping sports such as basketball and volleyball). Sever's: Athletes who play with cleats (excess grip in the ground) who push hard while running; also soccer and basketball players.
3. It is more common on the left, however, about 25% have it bilaterally.
4. The term "little league elbow" is used to describe a group of pathologic entities in and around the elbow joint in young throwers secondary to overhead throwing. Valgus stress results in lateral compression and medial traction on the elbow leading to the many types of injuries described in the text.
5. Tennis serving, football quarterbacks, javelin throwers, volleyball spikers.
6. A direct blow to the bony rim causing enough of an increase in intraorbital pressures to fracture the thin interior bones (usually the orbital floor).
7. CT scan, with special coronal views.
8. Topical beta blockers, cycloplegics, osmotic diuretics, carbonic anhydrase inhibitors.
9. The most severe complication is a rebleed. Limiting physical activity in children within the first 72 hours is important. This includes bedrest, no television or videogames, and bilateral eye patching.

Chapter XX.1. Puberty
Sherrel L. Hammar, MD

This is a 15 year old boy who is seen by his primary care physician for short stature and delayed sexual development. His past medical history is unremarkable except for asthma during early childhood, which has been well controlled. He is currently on no medications. He is an average student currently in the 9th grade and is the smallest in his class. He has been harassed by older classmates because of his size. His parents are concerned because Jim is becoming withdrawn and a "loner".

PMH: Pregnancy and delivery were uncomplicated. Birth weight and length were 3.86 kg (8.5 pounds) and 51 cm (20"), respectively. His HC was 35 cm. His immunizations are current.

Family History: His mother is 48 years old and in good health. Her height is 167 cm (50th %tile). Her menarche began at age 13.0 years. His father is 51 years old, also in good health. His height is 184.0 cm (75th %tile). His father's onset of puberty is not known but he was shaving regularly by age 15. There is one older male sibling age 18 who is in good health. His puberty began at age 11 years. There is no history of smoking, alcoholism, mental illness, drug abuse or learning problems in the family.

Exam: VS T 37.1, P 110, R 32, BP 100/60. Ht. 158 cm (3rd %tile), Wt. 42.0 kg. (10th %tile). He is pale and anxious but cooperative. His HEENT exam is normal. His chest is clear. Heart regular, no murmurs. His pulses are symmetrical and equal. There are no masses or areas of tenderness in his abdomen. Genitalia: Normal circumcised phallus, SMR (Tanner) pubic hair stage 1, genital stage 2. His testes are firm, 2.5 cm in length and 4 ml in volume. His scrotum is reddened and stippled. The remainder of his physical exam is unremarkable.

Lab: CBC: Hgb 13, WBC 9.5, normal differential, platelets 350,000. UA is normal. Bone Age: (left hand and wrist) 12.0 years. LH and FSH are decreased but normal for SMR stage 1-2.

Impression: Constitutional Short Stature, Delayed Puberty

Clinical Course: Over the next 6 months, pubic hair growth is noted. His testes enlarge to 3-4 cm in length and his height increases by 5 cm.

Puberty refers to the biological changes that lead to reproductive capability while adolescence generally refers to the psychosocial changes that occur. The sequence of events that occur during puberty are generally fairly predictable. The timing of these events, however may be highly variable.

Sexual Maturity Ratings (SMR), also known as Tanner stages, utilize pubic hair stages and breast development stages for females, and pubic hair stages and male genital development stages for males. Table 1 categorizes the pubic hair SMR stages for males and females. Table 2 categorizes female breast development SMR stages. Table 3 categorizes male genital development SMR stages, which are based on testicular size.

Table 1. SMR Pubic Hair Stages: Mean chronologic age (CA) and bone age (BA) in males and females (in years)

	Male CA	Male BA	Female CA	Female BA
I. None				
II. Sparse	12.2	13.5	10.4	11.5
III. Coarse, easily visible	13.5	14.2	12.2	12.2
IV. Confined to suprapubic area	14.2	14.2	13.0	13.2
V. Adult type on medial thighs	14.9	14.0		

Stage II-V = 2.7 yrs avg.

Table 2. SMR Female Breast Stages: Mean chronologic age (CA) and bone age (BA) in females (in years)

	CA	BA
I. No development		
II. Bud	10.9 (8.5-13.3)	10.5
III. Breast tissue beyond areola	12.2	12.0
IV. Secondary mound	13.2	13.5
V. Adult	14.0	15.0
Peak height velocity	12.2 (10.2-14.2)	12.5
Menarche	12.7 (10.5-15.5)	

Stage II to Stage III = 1.3 yrs avg.
Stage III to Stage V = 2.4 yrs avg.

Table 3. SMR Male Genital Stages. Mean chronologic age (CA) and bone age (BA) in males (in years)

	Testicular Length	Testicular Volume	CA	BA
I.	<2.5cm	<4mL		
II.	>2.5 cm	4-6 mL	11.2 (9.2-14.2)	11.5 (9.0-13.5)
III.	>3.0cm	6-10 mL	12.9	13.2
IV.	>4.0cm	10-15 mL	13.8	14.5
V.	>5.0cm	>15 mL	14.7	
Peak height velocity			13.9 (12.3-15.5)	14.5

Females initially show a deposition of adipose tissue and widening of the pelvis and changes in the contour of the hips. The first clinical sign is thelarche (the appearance of breast buds) and adrenarche (the appearance of dark straight pubic hair over the mons veneris, also called the mons pubis). These changes identify a SMR stage (or Tanner stage) II (see tables 1 and 2). Breast development over the next 4 years will proceed from breast stage II (secondary mound of breast tissue to adult breast stage V). Development of pubic hair starts about 1 year after breast budding and may take place over a 1.5 to 3.5 year period. During SMR stage 3, girls experience a very rapid increase in their height. The peak of their height growth (PHV=peak height velocity) should take place before the onset of menarche in most girls. Menarche occurs six months after the PHV and just prior to stage IV of breast development. Most western girls achieve their menarche around 12.4 to 12.8 years of age. African-American girls are maturing earlier.

Puberty in boys also follows a regular sequence of events, but lacks the clear cut landmarks such as breast development and menarche. In the male, the pubertal growth spurt is a late event starting about two years later than in females. The onset of pubertal changes however, are only about 6 months later than in females (see tables 2 and 3). Enlargement of the testes indicates the transition from genital stage I to Stage II, beginning at an average age of 11.5 years. Penile growth occurs about one year later. This is usually preceded by the appearance of pubic hair at the base of the phallus progressing through pubic hair stages II to V. Pubic hair stage III is followed by the appearance of axillary and facial hair growth. Testicular growth is completed anytime between 13.5 and 17 years of age. Growth of the penis reaches a SMR (Tanner) stage V between 12.5 and 16.5 years of age. Nocturnal emissions (wet dreams) may first appear during SMR stage III.

There is a common misconception that the difference between the onset of puberty in males and females is 2 years. This applies only to the growth spurt and not to pubertal (SMR) changes.

The patient described above is not only short statured but is delayed in his pubertal development. On the basis of the physical findings described, he would fit a presumptive diagnosis of constitutional delay of growth and maturation.

Boys with a constitutional delay of growth and maturation, usually have a normal birth weight and length, and progress along their normal growth centile for the first several years of life, following which, they begin to deviate and grow at or below the 3rd percentile throughout childhood. At the time when normal puberty should begin, there is often a marked fall off in growth (pre-adolescent dip) due to a diminished secretion of growth hormone. This transient fall in growth hormone is probably due to failure of sex hormone production and stimulation.

Skeletal maturation is usually delayed. When the bone age eventually reaches the skeletal age when puberty is expected, it is likely that early signs of sexual maturation will also appear, which is the stage of testicular enlargement (SMR genital stage II).

Often a familial pattern of pubertal delay is reported. The incidence of affected males is about 10%. Patients with constitutional delay in growth and maturation usually do not reach their "mid parent" or predicted height. Catch up growth is largely dependent upon the delay of bone maturation at the time of diagnosis, indicating that there may be a genetic or familial component to their short stature.

In most males, a watch and wait approach is indicated for six to twelve months. The patient presented could have been prescribed a short term course of testosterone or gonadotropins in order to stimulate sexual maturation and growth hormone production. In general, such treatment has been reserved for teenagers with significant behavior or psychological (self image) problems due to their delayed puberty.

In most cases, the evaluation of a patient suspected of delayed sexual maturity can be conservative. A thorough family history, physical examination, and assessment of sexual maturity stage will often show signs of early pubertal changes. The bone age is usually delayed and reflects the physical delays and the height age of the patient (the age corresponding to the 50%ile of the patient's actual height). Gonadotropins usually reflect the sexual maturity status of the patient. A chromosomal karyotype is indicated for all short statured girls who are delayed (for possible Turner syndrome) and for boys who are tall with small soft testes with or without delayed sexual maturity (Klinefelter's syndrome).

Table 4. Causes of Short Stature

- I. Constitutional Short Stature
- II. Primordial Dwarfism (intrauterine growth retardation)
- III. Endocrine Causes
  - A. Growth Hormone Deficiency
    1. Congenital
    2. Acquired
       a. Hypothalamic/Pituitary Tumors
       b. Head Trauma
       c. CNS infections
       d. Psychosocial Dwarfism
    3. Laron Dwarfism
    4. Hypothyroidism
    5. Syndromes of Short Stature
       a. Turner Syndrome (gonadal dysgenesis)
       b. Noonan's Syndrome
       c. Prader-Willi Syndrome
- IV. Chronic Disease
  - A. Heart Disease
  - B. Pulmonary
    1. Cystic Fibrosis
    2. Asthma
  - C. GI Disorders
  - D. Hepatic Disease
  - E. Renal
- V. Iatrogenic
  - A. Corticosteroids, anabolic steroids
  - B. ADHD meds

Table 5. Causes of Delayed Puberty

- I. Constitutional Delay in Growth and Maturation
- II. Hypogonadotropic hypogonadism
  - A. Central nervous system disorders
    1. Tumors
       a. Craniopharyngiomas
       b. Gliomas
       c. Germinomas
    2. Radiation Therapy
    3. Congenital Malformations
  - B. Isolated Growth Hormone Deficiency
    1. Kallmann's Syndrome
  - C. Miscellaneous Disorders
    1. Prader-Willi Syndrome
    2. Hypothyroidism
    3. Malnutrition
    4. Anorexia Nervosa
    5. Exercise amenorrhea
    6. Cushing's
    7. Diabetes
- III. Hypergonadotropic hypogonadism
  - A. Turner Syndrome
  - B. XX and XY gonadal dysgenesis
  - C. Polycystic ovary Syndrome
  - D. Noonan's Syndrome

Questions

1. What is the first objective physical sign of puberty in the male? In the female?
2. The difference in age between the initiation of pubertal (sexual) changes in the male and female is how many months?
3. What is the definition of delayed puberty? Precocious puberty?
4. What is the height age?
5. The best indicator of the biological age of the individual is?

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Answers to questions

1. Enlargement of the testes measuring greater than 2.5 cm in length and scrotal changes are the first signs of puberty in the male. The appearance of breast buds in the female indicate the onset of puberty.

2. There is approximately 6 months difference in the age of onset of sexual maturation in the female vs. the male.

3. Puberty is delayed when there is no sign of pubertal development by age 13 years in girls and 14 years in boys. Precocious puberty is secondary sexual development occurring before age 9 years in boys or 8 years in girls.

4. Height age is the age at which the height of the individual is equal to the height of 50 percent of a reference standard population by age and gender. This is done by taking the patient's height and finding the age, at which this height is the 50th percentile on an appropriate height grid.

5. The best indicator of the biological age of the individual is the skeletal age (bone age).

Chapter XX.2. Anabolic Steroids
Robert J. Bidwell, MD

This is a 17 year old male who has come to see you for his annual well-teen sports health evaluation. As with all your patients, you meet with him alone and discuss his physical and psychosocial health and development over the past year. He acknowledges no significant physical illness and feels he is developing appropriately. He reports getting along well with his parents and he is generally a "B" student at school. He is involved in his school's track team and also belongs to a paddling club. He denies any substance use. He is sexually active with his 16 year old girlfriend and reports using condoms consistently. He denies any major mood changes or suicidal ideation. His physical exam was completely normal.

Although he is unaware, you recently received a call from his father who had found pills in his son's room. He believes they may be steroids since he had overhead his son talking with other teammates about someone dealing in steroids at school. He asks you to bring this up with his son. When you specifically address steroid use, he admits that he and several of his friends on the track team have been using steroids regularly for the past 4 months. He believes it has increased his muscle mass and improved his appearance but admits he knows little about the potential side effects of steroid use.

Anabolic steroids, which are synthetic derivatives of testosterone, have legitimate uses in the treatment of male hypogonadism, chronic illness and other starvation or catabolic states. However, they also belong to a group of drugs known as "performance enhancers" (1). Their first use among athletes was in the early 1950s, most notably among male and female Soviet athletes competing internationally. The anabolic (tissue-building) effects of these steroids come from their binding to specific cellular receptors resulting in increased protein synthesis. In addition, they have an anti-catabolic effect by competitively binding to glucocorticoid receptors. The result is increased lean body mass (muscle) as well as increased muscle strength, especially if accompanied by a rigorous exercise regimen and adequate diet. These, in turn, can result in enhanced athletic performance. Their use is most common in football, wrestling, basketball, track and field, swimming, weight training and bodybuilding. Performance also may be enhanced through increased aggressiveness and endurance resulting from steroid use. Anabolic steroids do not improve and may actually limit aerobic capacity, agility and athletic skill. Other "performance enhancers" include human growth hormone (hGH), stimulants, diuretics and a variety of protein, vitamin and mineral supplements. Blood-doping (intravenous infusion of blood) is another technique used by athletes to improve performance. Some male adolescents take anabolic steroids not to enhance athletic performance but to improve their physical appearance through increased muscle mass and definition.

Studies of anabolic steroid use among high school students show a prevalence rate of 5-11 percent for males and 1.4-2.5 percent for females (2). A 1998 survey of junior high school students revealed that nearly four percent had used anabolic steroids (3). During the decade of the 1990s, anabolic steroid use among both males and females has increased (4).

Anabolic steroids can be taken orally or injected intramuscularly. Often both routes are employed simultaneously, a process known as stacking. Another pattern of use is megadosing, with doses up to forty times greater than therapeutic doses. Pyramiding is a third technique in which doses are increased then decreased on a cyclic basis.

Anabolic steroids are not difficult to obtain, even for high school students. Sources of the drug include friends, coaches, veterinarians and physicians. Anabolic steroids can be purchased over-the-counter in many foreign countries and brought back into the U.S. for distribution.

The use of anabolic steroids can result in increased muscle mass and strength. These attributes are highly desired by the adolescent user. However, many negative effects of chronic anabolic steroid use have been documented (Table 1 below). These primarily relate to its effects on growth and the hepatic, cardiovascular, and reproductive systems. Anabolic steroids can also have serious effects on a patient's psychological state, typified by violent mood swings ("roid rage"). Oral preparations are more hepatotoxic than injected forms, but with injection comes the risk of Hepatitis B and HIV (if contaminated or shared needles are used). Studies have shown that as many as 25 percent of users who inject steroids have shared needles (5). Anabolic steroid users are also more likely to use other drugs and experience their attendant risks. Most side effects of steroid use disappear on discontinuation of use. However, premature epiphyseal closure is irreversible and peliosis (purpura), hepatoma, baldness, clitoromegaly and voice changes will likely persist.

Because anabolic steroid use can have multisystemic effects as described above, the differential diagnosis would at first appear to be a lengthy one. However, a history of athletic involvement in sports where muscle mass is important coupled with an unusual degree of muscle development should place anabolic steroid use at the top of the differential diagnosis list. Testosterone-producing tumors may have masculinizing effects on both males and females, but usually result in muscle-wasting and other signs of chronic illness.

Once an adolescent who is using anabolic steroids has been identified, the pediatrician assumes the role of educator and counselor. Traditional drug treatment programs do not treat youths using anabolic steroids unless this use is part of a broader spectrum of substance use. Guidelines for the approach to the adolescent using anabolic steroids have been established by the American Academy of Pediatrics (2). In general, counseling should be provided in a confidential and non-judgmental manner. It is appropriate to acknowledge to the patient that anabolic steroids may, in fact, lead to increased muscle mass and strength. It is also appropriate to express an understanding of why athletes and others might want to increase muscle mass, strength and definition. This honest discussion of the "benefits" of steroid use must then be balanced with an honest review of the risks of use. Simply citing the negative effects is both dishonest and diminishes the physician's credibility in the adolescent's eyes. There is no evidence that scare tactics work in diminishing steroid use since the drive to excel athletically is so strong.

Pediatricians also have a role in prevention. At the individual patient level, screening questions and anticipatory guidance regarding anabolic steroid use should be a part of each well-teen visit. Adolescents who present with signs or symptoms suggestive of steroid use, even if not related to the presenting complaint, should be asked specifically about the possibility of anabolic steroid use at acute care visits. Adolescents can be counseled about alternatives for improving their strength and appearance through healthier diets and appropriate physical training. Discussions about the concept of "fair play" and the satisfaction coming from relying on one's natural abilities and hard work are reasonable, but will be counterproductive if they sound like lecturing.

At a community level, pediatricians can educate parents, schools and coaches about the prevalence and risks of anabolic steroid use among students. Drug screening programs at a school or team level are impractical and expensive.

Table 1. Negative effects of anabolic steroid use (2).

Musculoskeletal: premature epiphyseal closure, short stature, ligament and tendon injuries.
Hepatic: benign and malignant tumors, toxic hepatitis, peliosis hepatis, decreased HDL, increased LDL and cholesterol.
Cardiovascular: hypertension, stroke, thrombosis.
Male reproductive: decreased testosterone production, decreased testicular size, impotence, enlarged prostate.
Female reproductive: breast atrophy, clitoromegaly, menstrual changes, teratogenicity.
Other: deepened voice, acne, alopecia.
Psychological: severe anger outbursts, hallucinations, paranoia, anxiety, addiction.

Questions

1. True/False: Anabolic steroid use is usually effective in enhancing athletic performance.
2. Name the two most common routes of anabolic steroid administration. Which is the more hepatotoxic route?
3. In an adolescent using anabolic steroids who is at Sexual Maturity Rating (Tanner Stage) II, what is a major danger involving the musculoskeletal system?
4. In which patients should pediatricians consider the possibility of anabolic steroid use?
5. What is the role of the pediatrician in addressing anabolic steroid use?

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Answers to questions

1. True. One of the reasons it is difficult to dissuade competitive athletes from using anabolic steroids is that it can, in fact, result in increased lean body mass, muscle strength, and aggressiveness. These may, in fact, contribute to enhanced athletic performance.
2. Anabolic steroids may be taken orally or injected intramuscularly. Oral steroids are more hepatotoxic.
3. An adolescent in early puberty who uses steroids risks premature epiphyseal closure with resultant shorter stature than otherwise would be predicted.
4. Anabolic steroid use should be considered and addressed with all adolescent patients, male or female, athlete or non-athlete. Particular attention should be paid to those adolescents who have greater than expected muscle-mass development or in females with signs of masculinization.
5. On an individual level, pediatricians should, without lecturing, initiate an honest discussion of the risks and benefits of steroid use. They should ask all adolescents, and especially those with signs and symptoms of steroid use, about the possibility of using steroids. They also have a role in educating parents, teachers and coaches about the prevalence and dangers of anabolic steroid use.

Chapter XX.3. Substance Abuse
Anthony P. S. Guerrero, MD

This is a 16 year old female brought to the emergency room by her father, with the chief complaint that he thinks his daughter is using drugs and wants her to get treatment. The father reports that she has often been acting "high," with sleeplessness for several days in a row, unusual euphoria, pressured speech, increased activity (e.g., cleaning the bathroom), suspiciousness, and some aggressive behaviors. The pediatric resident begins to advise him that this behavior is typical of cocaine intoxication. However, with encouragement from the supervising emergency room physician, the resident gathers further history. She uses "ice," or "batu", roughly 2-3 times per week, smoking it by pipe. She obtains the drug from her friends. She admits to occasional marijuana use and weekend drinking of alcohol, without any history of blackouts, hallucinations, or incapacitating withdrawal symptoms. Although previously an above average student, she has, for the past year, been truant from school and is failing most of her classes. She has also run away from home on several occasions. She gives vague answers when asked about sexual history.

Her past medical history is otherwise negative. Family history is significant for a history of alcoholism and a possible psychotic illness. Her parents are divorced. There is no history of abuse or domestic violence.

Exam: VS T37.5, P 110, R18, BP 130/80. She is somewhat restless and guarded, with poor eye contact and brief answers. HEENT significant for slightly dilated pupils. Heart shows regular rhythm and elevated rate. Pelvic examination is refused. The remainder of physical examination is normal.

Labs: Urine toxicology positive for methamphetamine, negative for others, including alcohol. Electrocardiogram is significant for sinus tachycardia, otherwise normal.

Clinical course: Psychiatric consultation is obtained, and patient is briefly admitted involuntarily for psychiatric inpatient care. Diagnoses: Methamphetamine dependence and (via pelvic examination eventually performed by the consulting pediatrician) Chlamydia cervicitis. She is discharged to an adolescent substance abuse treatment program.

Substance use is common among adolescents in the United States (1). By the end of high school, 90% of adolescents have tried alcohol and 40% have tried an illicit substance. Among 17 to 19 year olds, the lifetime prevalence of alcohol abuse and dependence (beyond just experimentation) is 32%, while the lifetime prevalence of drug abuse and dependence is 10%. Consequently, pediatricians will often need to be involved in the evaluation and management of: substance use disorders, medical problems related to substance use, and/or other medical problems which may go under recognized or under managed in this high risk population.

Substance abuse is defined as a maladaptive pattern of substance use with clinically significant levels of impairment or distress, while substance dependence requires a substantial degree of substance use involving withdrawal, tolerance, and loss of control over use (2). Risk factors for these substance use disorders include genetic/family predisposition (e.g., with positive family history); exposure to substance use via family or peers; childhood psychiatric conditions; and poor academic performance. The dopamine reward pathway has been implicated in the pathophysiology of substance addiction (3). Contrary to what some may believe, there is no evidence that stimulant treatment of Attention Deficit Hyperactivity Disorder increases risk for substance abuse. In fact, a recent study suggests otherwise, possibly because of the benefits of treatment on behavior and academic performance (4).

Alcohol and sedatives (benzodiazepines, barbiturates, and related compounds) are grouped together because they facilitate binding of gamma amino butyric acid (GABA), an inhibitory neurotransmitter, to neurons. Benzodiazepines and barbiturates may sometimes be referred to as "downers," and are often available in pill form.

Cocaine and methamphetamine both work via an increase of catecholamines, leading to the psychiatric and general physical symptoms as described in the case above. Of interest, chronic use of methamphetamine, via toxic effects on the brain, may also result in a chronic psychotic disorder, even beyond cessation of its use. Patients who present with this syndrome may, on functional brain imaging, show a "Swiss cheese" pattern, with significant areas of hypo-functioning. These drugs may be inhaled, smoked, or (less commonly) taken intravenously.

Hallucinogens, including D-lysergic acid diethylamide (LSD) and various others (mostly from plants) exert their hallucinogenic effects via serotonin receptors. These may be administered via various routes. Of interest, "ecstasy", or 3,4-methylenedioxymethamphetamine, works via the catecholamine and serotonin systems and may produce amphetamine-like effects as well as feelings of closeness to people and sensory sensitivity. Symptoms of catecholamine excess as well as dehydration are possible complications of its acute use. This drug may be taken orally, inhaled, or injected intravenously.

Inhalants, including glue, paint thinner, and other solvents, likely cause disruption of neuronal and other cell membranes, leading to potential complications of encephalopathy and cardiac arrhythmias. These agents, being relatively accessible, may be abused by younger adolescents.

Marijuana exerts its intoxicating effects via tetrahydrocannabinoid receptors in the brain. It is most commonly smoked.

Opioids, including heroin and controlled prescription medications, working via the opioid receptors in the brain, may result in respiratory depression, miosis, analgesia, and constipation during intoxication and autonomic hyperactivity, gastrointestinal hyperactivity, and significant discomfort during withdrawal. Heroin use may be associated with any of the medical complications (e.g., HIV disease, endocarditis, localized skin infections) associated with intravenous drug use and injections using contaminated needles.

Phencyclidine, or PCP, exerts its effects via the receptor of N-methyl-D-aspartate (NMDA), an excitatory neurotransmitter, and other receptors. Intoxication may result in diminished responsiveness to pain, severe muscle rigidity, and hyperthermia. It is most commonly smoked, but may be administered via other routes as well. Because it is more rapidly excreted in acidic urine, acidifying agents may be considered in detoxification.

Other drugs: Gamma-hydroxy-butyrate, or GHB, can have the extremely serious side effects of seizures and coma. It exerts its effects via the dopamine and opioid receptors. It is often available in liquid form.

The pediatrician must always consider substance use as a possibility, and must be prepared to manage any life threatening effects of either intoxication or withdrawal. All substances can potentially cause acute allergic and/or other serious idiosyncratic reactions, which should be managed accordingly, with priority attention always given to airway, breathing, and circulation.

Intoxication with alcohol, especially in a relatively alcohol naive adolescent, may result in a life threatening respiratory depression. Hence, medical admission with close monitoring of respiratory status may be indicated. Likewise, withdrawal from alcohol or other sedatives (e.g., benzodiazepines, barbiturates) may also be life threatening, although delirium tremens is fortunately not as common in adolescents as it is in older adults. Careful monitoring of vital signs, prescription of thiamine and multivitamins, and implementation of

benzodiazepine-based protocols for management of withdrawal (5) are indicated. To assess withdrawal risk, the clinician should take a careful history to include pattern/regularity of use, timing of last use, severity of past withdrawal symptoms, etc.

The autonomic hyperactivity resulting from cocaine or methamphetamine intoxication may lead to life threatening arrhythmias or ischemia of the brain, heart, or intestines. Close cardiorespiratory monitoring and an electrocardiogram may be indicated.

Acute agitation, delirium, and/or psychosis resulting from cocaine, methamphetamine, hallucinogen, or marijuana intoxication may be managed using a quiet, supportive setting and frequent reorientation to person, place, and time. Although substance use may result in altered mental status, general medical conditions (e.g., intracranial bleed) must always be ruled out, as they unfortunately do occur in youth who use substances. Benzodiazepines may be used for agitation. High potency antipsychotics (e.g., haloperidol) may be used for symptoms of delirium or psychosis with agitation. However, antipsychotics should be avoided in cases of alcohol or sedative withdrawal, as these medications may lower the seizure threshold (in such cases, benzodiazepines should be used). Low potency antipsychotics (e.g., chlorpromazine) should not be used in cases of PCP intoxication, as the additive anticholinergic effects may worsen the delirium.

Because youth with substance use disorders are often at risk for poor health, the physician should perform a careful history, physical examination, and laboratory evaluation and thoroughly address any other concerns that may be detected. In addition to addressing physical health concerns, the physician should employ the bio-psycho-social approach (discussed in the chapter on suicide and violence) to comprehensively care for the adolescent with a substance use disorder, and should have a low threshold for consulting a child and adolescent psychiatrist.

Often, the primary care physician can be a credible source of information about the long-term side effects of substance abuse, such as liver damage from alcohol use, serious "brain damage" from inhalant use, and lung cancer from tobacco or marijuana use. Also, the primary care physician may have significant familiarity with the family history, and can be helpful in "personalizing" the information for the adolescent (e.g., discussing relatives who died of medical sequelae of substance abuse or whose lives were destroyed by addiction).

One substance abuse problem commonly encountered and managed by the primary care physician is cigarette smoking and nicotine dependence. The physician should become comfortable with assessing stages of motivation (e.g., contemplation versus pre-contemplation) and practicing the 5 A's of asking (about tobacco use), advising (quitting), assessing (willingness and possible barriers), assisting (e.g., setting a quit date), and arranging (follow-up) (6).

Above all, physicians should be compassionate and professionally responsible towards adolescents with substance use disorders. They should recognize substance abuse as a medical condition and should respect the seriousness of its complications and co-morbidities.

Questions

1. The prevalence of alcohol abuse and dependence among 17 to 19 year olds in the United States is closest to: a) 1%, b) 10%, c) 30%, d) 50%, e) 90%
2. True/False: Stimulant treatment of Attention Deficit Hyperactivity Disorder increases risk for future substance abuse.
3. True/False: Death may occur during intoxication with alcohol or an illicit substance.
4. True/False: Death may occur during withdrawal from alcohol or an illicit substance.
5. Match the following substances with their associated syndromes:

a. Barbiturates	i. Severe encephalopathy
b. "Ecstasy"	ii. Lung cancer
c. Inhalants	iii. Rhabdomyolysis during intoxication
d. Marijuana	iv. Wanting to touch/be touched during intoxication.
e. Methamphetamine	v. Seizures during withdrawal
f. PCP	vi. "Swiss cheese" appearance on functional brain imaging

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Answers to questions

1.c, 2.F, 3.T, 4.T, 5.a-v; b-iv; c-i; d-ii; e-vi; f-iii

Chapter XX.4. Adolescent Suicide and Violence
Anthony P. S. Guerrero, MD

This is a 17 year old male who is brought to the emergency room by his family. Earlier, he got into an argument with his girlfriend and began to ingest several ibuprofen tablets in front of her. He says he didn't really premeditate the act, and he denies having written a note. He has been feeling very depressed and upset for the past several months. Family members also note that he has been moody and explosive. In fact, one week ago, he was referred to the school based police officer because he threatened to go on a shooting rampage using his family's hunting rifle. He has been doing worse in school for the past semester and is at risk of not graduating. Reportedly, his teachers have complained that he is disruptive with his non-stop talking and "giggliness". His family suspects that he may be using marijuana. Apparently, he had been referred for a mental health evaluation at the school, but his family decided not to keep the appointment.

His past history is otherwise negative. Family history is significant for alcohol abuse in the biological father, who tended to use corporal punishment on the children.

Exam: His vital signs, including blood pressure, are normal. He is superficially cooperative, though restless and fidgety. His eye contact is poor, and he frequently looks to the side during the conversation. Speech is mumbled and rapid. Affect is angry. He thinks that what he did (with the ibuprofen) was "stupid" but does not elaborate very much. Even though he recognizes his difficulties in school, some of his plans seem a bit unrealistic (e.g., becoming a decorated fighter pilot in the military). Physical examination is otherwise unremarkable.

Laboratory studies: Urine toxicology screen positive for cannabis only. Other screening labs, including tests of thyroid function, are normal.

Psychiatric consult obtained. Provisional diagnoses: Bipolar disorder (not otherwise specified), marijuana abuse. A decision is made to admit the patient for psychiatric care. After discharge, it is discovered that his school is very nervous about accepting him back, for fear that he might become violent again.

In the United States, homicide and suicide are the second and third leading causes of death among teenagers (1). Consequently, all health professionals caring for children and adolescents must give high priority to the prevention, early identification, and early referral for these significant causes of morbidity and mortality. For the purposes of this chapter, suicide and violence will be considered together, as violence to others is often a risk factor for violence to self.

Major risk factors for completed suicide in adolescents include previous suicide attempts, mood disorders, and substance abuse (2). Hence, primary care physicians should be attentive to signs of substance abuse (discussed in another chapter) and possible symptoms of depression, which include a persistently sad mood, lack of enjoyment, sleep/appetite/energy level disturbances, and/or difficulties concentrating and performing adequately in school. Youth who present with a major depressive episode have about a 30% risk (3) of going on to develop a bipolar disorder, which often has a "mixed" (e.g., depressive and hypomanic/manic symptoms coexisting) and/or "rapid cycling" presentation in this age group. Hence, other symptoms which should lead the physician to suspect a mood disorder include irritability, "mood swings," angry outbursts, grandiosity, rapid speech, increased motor activity, and impulsive behavior (which the patient described above seems to have). Often, these youth present in juvenile correctional and other legal settings and would otherwise be diagnosed as having a "conduct disorder". Biederman et al's findings (4) of significant co-morbidity (i.e., correlation) between "conduct disorder" and treatable mood disorders should prompt the primary care physician to carefully consider mood disorders in any "delinquent" adolescent, and to appropriately refer for psychiatric care.

All physicians should be familiar with screening for suicidality and assessment of the suicidal patient. Suicidality is often assessed in the context of routine health maintenance examinations for teenagers. One may enhance the sensitivity of inquiry about suicidality by "leading into" the topic and then definitively asking the questions: e.g., "How do you feel most of the time? Are there ever any times when you would say you feel depressed? How intense does it get? Does it ever get to the point when you think that life isn't worth living anymore? Did you ever make a plan to end your life? Do you have thoughts about ending your life right now?" In the patient who is acutely suicidal, the following items are important to assess: previous attempts, command auditory hallucinations (voices encouraging suicide leading to the attempt), intoxication during the attempt, stressors, and symptoms of mood disorders.

In the patient who has attempted suicide (such as the patient described above), additional items of value are: premeditation, note writing, giving away of objects, setting/context of suicide attempt, how discovered (e.g., in front of others versus all alone, with no expected chance of discovery), appreciation of lethality (e.g., might have thought that ibuprofen could kill instantly; or might have thought that iron pills were harmless), how one feels now, and what has changed since the suicide attempt.

The history and physical should include a thorough psychosocial history (including exposure to violence and abuse) and should be complete enough to rule out any medical conditions which could manifest as a mood disorder (e.g., thyroid disorders, EBV infections, etc.)

The risk factors for, and the assessment of violence, are similar to what is described above (e.g., past violence, intoxication during violence, etc.). There is also a significant emphasis, nationally, on the prevention of violence. The Commission for the Prevention of Youth Violence (5) identifies prevention of youth violence as a high priority, and lists several objectives: 1) to support the development of healthy families; 2) to promote healthy communities; 3) to enhance services for early identification and intervention for children, youth, and families at risk for or involved in violence; 4) to increase access to health and mental health care services (which the family described above had difficulty with); 5) to reduce access to and risk from firearms for children and youth (a priority for the patient described above); 6) to reduce exposure to media violence; and 7) to ensure national support and advocacy for solutions to violence through research, public policy, legislation, and funding. The American Academy of Pediatrics (1) also emphasizes avoidance of corporal punishment (which could have been important for this case).

Management of a case such as the one described above, mandates a comprehensive bio-psycho-social approach. From a biological perspective, the patient may have a genetic predisposition to a mood disorder amenable to a mood stabilizer medication. However, the patient also uses substances which could affect mood; therefore, maintenance of a drug free state is also important for treatment. Other medical conditions should be ruled out. From a psychological perspective, recent stressors may include academic difficulties and difficulties in his relationship. Furthermore, poor coping skills and exposure to family violence may increase his risk of committing a violent act. He may therefore benefit from: an educational evaluation to identify and address any possible learning difficulties; supportive psychotherapy; and training in anger management. From a social/cultural perspective, dysfunction in the home may have led him to seek support from substance abusing peers. Culturally sensitive services for the family would also be key to effective treatment, keeping in

mind the possible language and cultural barriers to timely mental health intervention. The family and school should be educated on community resources for violence (e.g., suicide and crisis hotline). Finally, firearms and other potential agents of violence should be removed from the home.

Understandably, even with optimal, comprehensive management, this will be a significant challenge for families, schools, and communities. Prevention is therefore an important task for all healthcare professionals.

Questions

1. True/False: Mood disorders should be seriously considered in all teenagers with disruptive behaviors and decline in academic performance.
2. True/False: Otitis media, meningitis, and pneumonia are the top leading causes of death in children and adolescents.
3. True/False: The comprehensive bio-psycho-social approach to suicide/violence prevention is a potentially life saving skill that all physicians should practice.
4. True/False: Physicians should liberally use antidepressants to treat any child or adolescent who appears depressed.
5. True/False: A teenager who intentionally ingests a large yet non-toxic dose of a non-toxic medication may still be at significant risk for suicide.
6. True/False: Physicians caring for teenagers with disruptive behaviors should attempt to minimize contact with the teenagers' families.
7. True/False: In the future, pediatricians will likely have little role in violence prevention, because there are projected to be enough child and adolescent psychiatrists to fulfill this role.

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Answers to questions

1. T
2. F
3. T
4. F. Compared with adults, children and adolescents presenting with a major depressive episode are at relatively higher risk of actually having a bipolar disorder. Significant caution must therefore be exercised in prescribing an antidepressant, which may precipitate mania or hypomania. The author advises that child and adolescent psychiatric consultation be sought.
5. T.
6. F. Often, working with the family is a key component of treatment.
7. F. Currently, there are only 6300 child and adolescent psychiatrists in the United States, where the estimated need is for up to 30,000. The population of children is expected to grow 40% in the next 50 years (6). Pediatricians will likely play a very significant role in insuring the psychosocial health of children.

Chapter XX.5. Eating Disorders
Robert J. Bidwell, MD

This is a 16 year old female who is brought to your clinic for her annual well teen exam. She denies any physical complaints, except for an occasional cold. Specifically, she denies any history of fatigue, fever, appetite or weight change. She is active and a review of symptoms is completely negative. A psychosocial (HEADSS) screening interview reveals no significant disagreements with her parents. She is a nearly straight "A" student at a public secondary school. She smokes an occasional cigarette but acknowledges no other substance use. She denies sexual activity with others and denies any history of abuse or suicidal ideation.

On physical exam, you note that she has lost 9 kg (20 lbs) since her last well teen exam a year ago. Her height is at the 50th percentile for age and her weight is now at the 10th percentile for age. Other than being very thin, the only other abnormality in her physical exam is a heart rate of 44 beats per minute. She had normal dentition, no lanugo hair, and a Sexual Maturity (Tanner) Rating of V. She denies any feeling of being too thin or too fat.

On a separate interview with her parents, you discover that they have been concerned about her losing weight since she began "eating healthier" over the past several months. She also seems "almost obsessive" in her physical activity, taking part in paddling, track, tennis and aerobic exercises at home. They believe she is no longer having menstrual periods. There has been no evidence of any binging or purging behaviors.

Eating disorders include anorexia nervosa, bulimia nervosa, binge-eating disorders and a number of disordered eating variants. The Diagnostic and Statistical Manual IV (DSM-IV) criteria for anorexia nervosa include an excessive concern with body weight and shape, an intense fear of gaining weight and an obsessional preoccupation with food and eating (1). Additional criteria include either excessive weight loss or failure to gain weight as expected in a pubertal child, accompanied by secondary amenorrhea or a failure to achieve menarche. Bulimia nervosa involves repeated episodes of binge eating, often accompanied by purging (self-induced vomiting, and laxative or diuretic use). Binge eating disorder consists of repeated consumption of very large amounts of calorie dense foods in a short period of time without subsequent purging. Variant eating disorders would include those in which an individual does not express dissatisfaction with weight or body shape or in which menstrual periods remain unaffected by weight loss. Anorexia nervosa and bulimia nervosa appear to represent a spectrum of disordered eating. At least half of the patients with anorexia nervosa engage in binge eating/purging and many patients with bulimia nervosa experience periods of significant caloric restriction.

It is believed that anorexia nervosa and bulimia nervosa have existed in Western societies for centuries. However, there has been an apparent increase in both since the late 1960's. They appear to be more prevalent in modern industrialized societies throughout the world. In the U.S., they occur in all socioeconomic classes and ethnic groups. Anorexia nervosa typically has an onset in adolescence or in early adulthood and is more common in females, with a prevalence rate of about 0.5% among 15 to 19 year old adolescent girls (2). The prevalence among adolescent males is much lower, although males make up as much as 40 percent of individuals with binge eating disorders. The prevalence of bulimia nervosa is less certain, but surveys indicate that 10 to 50 percent of young females engage in periodic self induced vomiting or binge eating. While about 3 percent of females have anorexia nervosa, bulimia nervosa or binge eating disorder based on strict DSM-IV criteria, at least 20 percent are considered to have some degree of disordered eating. This fact is important because the clinician should be prepared to intervene early, before all DSM-IV criteria are met.

The cause of eating disorders is multifactorial (3). Genetic predisposition, neurochemical factors, psychological factors and sociocultural influences all have been implicated in the onset of disordered eating.

It is also important to recognize the high incidence of psychiatric comorbidities among patients with eating disorders. These include mood disorders, obsessive-compulsive traits, perfectionist traits, social isolation, and impulsive tendencies (e.g., related to sex and drugs).

Signs and symptoms related to anorexia nervosa are primarily those resulting from starvation and malnutrition, and can affect nearly every organ system. For patients engaged in bulimic as well as restrictive eating behaviors, additional signs and symptoms related to binge eating and purging may be present. The most frequent and obvious physical sign of anorexia nervosa is significant weight loss leading eventually to profound cachexia. Other frequent signs include bradycardia, cardiac arrhythmia, hypotension, hypothermia and dehydration. Dry skin, brittle hair, and lanugo hair are also frequently noted. While many patients may deny any symptoms, despite significant cachexia, some will acknowledge weakness, fatigue, lightheadedness, headaches, palpitations, abdominal pain, constipation, cold intolerance and amenorrhea. Some patients will not express a distorted body image early in treatment, saying their weight loss is due to forgetting or being too busy to eat. However, as treatment begins and weight gain occurs, the underlying fear of gaining weight often becomes very evident. Pubertal delay and bone fractures due to osteopenia are possible, although infrequent sequelae to prolonged starvation. Laboratory studies, which are frequently normal, may reveal anemia, leukopenia, thrombocytopenia, hypercholesterolemia and mild elevation of hepatic enzymes. Hyponatremia secondary to water-loading is not uncommon.

Patients with bulimia nervosa are frequently normal weight for height or may be overweight. Those with periodic restriction may experience dramatic fluctuation in weight. Many patients with binge eating and purging behaviors may have a completely normal physical exam. Those signs and symptoms generally associated with these behaviors include dental erosions, parotid swelling, pharyngitis, chest pain (esophagitis), abdominal pain, hematemesis, and calluses or abrasions on the dorsum of the hand from self-induced vomiting. With significant purging behavior (vomiting, laxative, or diuretic use) electrolyte abnormalities, usually reflecting a hypochloremic hypokalemic metabolic alkalosis, and dehydration are common.

The differential diagnosis of weight loss in an adolescent is long (4). It includes malignancy and a variety of chronic illnesses including diabetes mellitus, hyperthyroidism, malabsorption syndromes, systemic lupus erythematosus, inflammatory bowel disease, and psychiatric disorders such as major depression and substance abuse. However, in most cases, information gathered from the history, physical examination and evaluative studies makes the diagnosis of anorexia nervosa relatively easy. For example, a patient (or patient's parents) who gives a history of a daily diet of only lettuce, tomatoes and rice cakes and who, despite a 10 kg (25 lb) weight loss, reports running 10 miles three times a week, is unlikely to have cancer or any of the other disorders listed above. On the other hand, it is important to remember that a patient with disordered eating may also develop diabetes or hyperthyroidism.

The differential diagnosis of binge eating with purging is much shorter, but may include other psychiatric conditions. If a patient denies willfully induced vomiting, the differential diagnosis includes a variety of gastrointestinal and metabolic disorders. Nevertheless, these latter conditions do not usually involve binge eating or lead to the kind of surreptitious vomiting engaged in by adolescents with bulimia nervosa.

In approaching the differential diagnosis it is important not to rely only on the adolescent patient's history. Many patients with anorexia nervosa will not report feelings of being fat or desiring to lose weight. Similarly, most patients with bulimia nervosa initially deny any bulimic behaviors. Parental observations of the patient's eating and purging behaviors or expressions of dissatisfaction with weight or body shape are invaluable on these cases.

Having made the diagnosis of an eating disorder, the first decision in treatment is whether the patient is in a life-threatening situation that requires either medical or psychiatric hospitalization. Medical hospitalization is generally indicated if there is evidence of significant cardiac compromise reflected in significant bradycardia, arrhythmia or hypotension. Electrolyte abnormalities such as hypokalemia or hyponatremia also place the patient at significant risk. Electrolyte disturbance and dehydration are relatively easy to correct through intravenous fluid and electrolyte supplementation. Continuous cardiac monitoring is also available in the hospital setting. Whether treatment begins in an ambulatory or an inpatient setting, an immediate goal is to increase nutrient intake. This can be done orally with a carefully devised meal plan or, if this is refused, through nasogastric feedings or hyperalimentation in the hospital setting. Treatment usually involves institution of an "Eating Disorder Protocol" in which normalized eating and weight gain is rewarded with increased privileges and non-compliance results in removal of privileges or hospitalization. The protocol also provides incentives for decreasing bulimic behaviors.

The treatment team often includes a psychiatrist, a pediatrician, a dietitian as well as the patient and her or his family. Because eating disorders are chronic in nature, the eating disorder team has a long term commitment to work with the adolescent patient and her/his family. The role of the pediatrician is to regularly monitor the patient's physical status during the stage of refeeding and weight gain. The dietitian provides counseling on appropriate nutrition and structural goals and guidelines to assure this occurs. The psychiatrist provides supportive care during the early stages of refeeding, and later begins the important work of facilitating increased self understanding as to the origins of the patient's disordered eating and provide therapy aimed at addressing those issues (5).

The long term prognosis for adolescent patients with anorexia nervosa is guarded at best (6). A recent review of follow-up studies of patients with this disorder found that only 44 percent had a good outcome (normalized weight for height and return of menstrual periods). Twenty-four percent had a poor outcome (failure to achieve normal weight for height and continued menstrual irregularities). Twenty-eight percent had an intermediate prognosis between "good" and "poor." Mortality was 5 percent overall. Suicide is the most frequent cause of death in patients with anorexia nervosa, followed by cardiac arrest and other medical complications related to starvation and/or binging or purging. The best prognosis occurs in patients with early onset of the disorder, less weight loss, no purging behavior, and healthy family functioning prior to onset of the disorder. Anorexia nervosa is often accompanied by other psychiatric conditions, and studies have found that patients responding well to treatment for their eating disorder may continue to experience depression, anxiety, obsessive-compulsive traits, social phobia and substance abuse.

Prognosis related to bulimia nervosa is less certain since many individuals with this disorder do not enter treatment. There is some evidence that even without treatment the rate of spontaneous remission may be as high as 30 to 40 percent over a one to two year period. With treatment, a positive outcome may be as high as 50 to 70 percent, although the relapse rate may also be high. One study of patients with bulimia nervosa who had successful results from intensive treatment showed that 60 percent continued to have good results at 6 years following treatment (7). Mortality was only 1 percent. Death is generally related to cardiac effects of hypokalemia due to purging behavior. Prognosis may be poor for patients with more frequent vomiting prior to entering treatment.

Questions

1. What is the leading cause of death in patients diagnosed with anorexia nervosa?
2. What is the most likely electrolyte abnormally in patients with bulimia nervosa who engage in self induced vomiting?
3. Name three indications for medical hospitalization of a patient with an eating disorder.
4. A teenaged female reports feeling healthy, denies feeling fat, and has normal menstrual periods. However, she has evidenced a 20 lb. weight loss. What is the most likely diagnosis?
5. Name six possible conditions or disorders on the differential diagnosis of excessive weight loss in an adolescent.
6. Which disorder is most likely to present with a normal physical exam, anorexia nervosa or bulimia nervosa?

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Answers to questions

1. Suicide is the leading cause of death in anorexia nervosa. The second highest cause of death is cardiac arrest.
2. Patients who self induce vomiting are most likely to develop a hypochloremic hypokalemic metabolic alkalosis.
3. Three indications for hospitalization of a patient with anorexia nervosa include: a) electrolyte abnormalities (hypokalemia, hyponatremia), b) cardiovascular abnormality (bradycardia, arrhythmia, hypotension), c) inability or refusal to engage in outpatient treatment.
4. The most likely diagnosis is anorexia nervosa. The point is that the most likely cause of significant weight loss in an adolescent female is an eating disorder, even if DSM-IV criteria are not completely met.
5. Disorders other than anorexia nervosa in the differential diagnosis of excessive weight loss in an adolescent include malignancy, diabetes mellitus, hyperthyroidism, malabsorption syndromes, systemic lupus erythematosus, inflammatory bowel disease, depression and substance use.

6. Bulimia nervosa is more likely to present with a normal physical exam. By definition, anorexia nervosa must show weight loss or a failure to gain weight appropriately during puberty.

Chapter XX.6. Adolescent Sexuality
Robert J. Bidwell, MD

Case 1: This is a 17 year old male who has been in a year-long relationship with his 16 year old girlfriend. Their relationship includes sexual activity, including both vaginal intercourse and oral sex. They use condoms consistently, citing a wish to avoid pregnancy and sexually transmitted infections (STIs). They both say their relationship is mutually consensual and fulfilling. They are doing well at school, have good relationships with their family and peers, and have plans to attend college next year. Marriage has not been discussed although they see their relationship as a long-term commitment.

Case 2: This is a 14 year old female who was sexually assaulted by her uncle between ages 8 and 11. At age 12 she began to skip classes at school and "cruise" with friends at the beach. A year later she was introduced to "ice" (methamphetamines) and also used cocaine, alcohol and marijuana on a weekly basis at "hotel parties." She has met many of her sexual partners, usually older males, at these parties. She rarely uses condoms and has had chlamydia cervicitis once. She is not sure if she has ever been pregnant; but admits she would like to become a mother. She is not interested in learning more about contraception or STI prevention at this visit.

Case 3: This is a 16 year old female who is seeing you for her annual well-teen evaluation. In interviewing her about sexuality, she says she has never been sexually active. Although she has dated boys, she acknowledges a growing awareness of her sexual attraction to other girls and believes she may be a lesbian. She is hoping you can provide more information to help her better understand her feelings.

Sexuality is one of the most fundamental aspects of who we are as human beings. It is directly related both to an individual's physical as well as psychosocial well-being. It also is multidimensional in nature, referring not only to sexual behaviors but also to attractions, fantasies, affiliations, sexual orientation, and gender identity. Issues related to sexuality, particularly adolescent sexuality, are often controversial. In our pluralistic society, attitudes about adolescent sexuality differ not only by ethnicity, socioeconomic status, religion, and geographic region, but also can vary widely within individual families and communities. It is always a "hot topic" and one that health care providers will be required to address in their daily practice with adolescents and their families.

Human sexuality begins in infancy and continues through old age. However, with the beginning of puberty, there clearly is a quantitative change in the experience of sexuality by the developing child. The process has been described as a "sexual unfolding", that is the evolving expression of sexual feelings and experiences whose strongest roots are established in early infancy and childhood. This sexual "unfolding" is influenced by hormonal and physical changes, as well as psychosocial changes shaped by individual experiences and societal influences. Sexual development includes an adolescent's increasingly better understanding of who he/she is as a sexual being. This is accomplished in part through the acceleration of sexual exploration both with self and others. In general, pediatrics in the Western world feels that such experimentation is a normal and healthy part of adolescent development. However, there still remains some controversy, even within pediatrics, around what specific feelings and behaviors are developmentally appropriate.

Sexual development is intimately connected to the stages of adolescent development. In early adolescence (approximately 10 to13 years old) there is a significant increase in sexual feelings and preoccupations. These may be directed toward the same or opposite sex. There is often an increase in sexual self-exploration, including masturbation, which is considered a normal sexual behavior. Nocturnal emissions ("wet-dreams") occur in males and menarche in females, signifying the onset of reproductive capacity. Some early adolescents may engage in same or opposite-sex exploration. These do not necessarily reflect eventual sexual orientation. These sexual experiences are usually more experimental and self-focused than those of older adolescents.

Middle adolescence (approximately 14-16 years old) is often the hallmark of adolescent sexuality. Pubertal changes are nearly complete and there is significant increase in both same and opposite sex preoccupation and activity. With an increased understanding of their sexual selves, middle adolescents are more able to establish longer-term relationships and understand that intimacy involves more than simply sexual activity.

In late adolescence (approximately 17 to 19 years old), preoccupation with sexuality and the percentage of teenagers who are sexually active continue to increase but the older adolescent is, in general, able to bring a greater commitment and mutuality to his/her relationships. The late adolescent is also more future-oriented and often begins to consider what sorts of qualities, sexual and otherwise, he/she considers desirable in a potential spouse or life-partner. The "sexual unfolding" outlined above is a lifelong process and does not, of course, end at age 19. It is, in fact, a lifelong process.

While all adolescents address issues of sexual development, more than half abstain from sexual intercourse until age 17. However, research has demonstrated that some of these "abstinent" teenagers may engage in a variety of potentially risky sexual behaviors with others. These include mutual masturbation, fellatio, cunnilingus and anal intercourse. The Centers for Disease Control's (CDC) 2001 Youth Risk Behavior Survey, an anonymous survey of 9th to 12th graders in all 50 states, indicates that within this grade range, 46 percent acknowledge sexual intercourse, 14 percent have had four or more sexual partners, and 33 percent have had intercourse during the three months prior to the survey. Among those students who reported sexual intercourse, 33% had not used a condom and 82% of females had not used birth control pills during their most recent sexual intercourse. Despite this evidence of significant adolescent sexual activity, positive trends have appeared in the CDC data over the past decade. For example, the percentage of students reporting sexual intercourse has dropped from 54% to 46% between 1991 and 2001. The percentage reporting four or more partners has decreased from 19% to 14% and the use of condoms at most recent intercourse has increased from 46% to 58% during that ten-year period.

One of the reasons that health professionals are concerned about the high percentage of adolescents engaged in sexual behaviors is that these behaviors often entail significant risks to physical and psychosocial health. Early pregnancy and sexually transmitted infections are two of the primary risks inherent in adolescent sexual activity. Pregnancy occurs at a rate of 80 per 1,000 females aged 15 to 19. For the same age range, the birth rate is 50 per 1,000 and the abortion rate (intentional termination of pregnancy only) is 28 per 1,000 females.

Adolescent pregnancy and birth rates have remained stable over the past decade. The rate of chlamydia infection is 1,132 per 100,000 adolescents aged 15 to 19. For the same age group, the rates for gonorrhea and syphilis infections are, respectively, 572 and 6 per 100,000 persons. The fact that these rates are far greater than those of Western European countries with similar rates of adolescent sexual activity most likely reflects U.S. adolescents' lower use of condoms and contraceptives. This may be due, in part, to cultural factors as well as health and educational policies at the federal and local levels that limit adolescents' access to information and services related to sexual and reproductive health.

Adolescent sexual decision-making is a very complex phenomenon. Research has demonstrated that the early onset of sexual activity with others is usually accompanied by other risk behaviors, such as substance use, school problems, and parent-teen conflict. It is also highly associated with a history of physical and sexual abuse, both inside and outside the family. In short, biological, social, familial, and experiential factors all play a part in each adolescent's decision to be sexually abstinent or become sexually active. If an adolescent does become sexually active, these factors also influence the ability to engage in "safer sex" practices. In general, the earlier the age of sexual initiation the more likely there are associated risk factors and a history of significant childhood abuse. The initiation of sexual activity during later adolescence is more likely to represent a normative process with fewer associated risks. The multitude of factors influencing an adolescent's decision to be abstinent or sexually active, likely is one of the reasons that "abstinence-only" sexuality curricula have been less effective in preventing adolescent sexual risk-taking than "comprehensive" sexuality curricula. The latter interventions encourage abstinence as the safest choice but recognize that some adolescents will choose to be sexually active and should be provided the information and skills they need to make that activity as safe as possible.

One of the most neglected areas related to adolescent sexuality has been that of sexual orientation. During puberty, approximately 3 to 10 percent of adolescents begin to recognize their lesbian or gay (homosexual) sexual orientation. An even greater percentage may be bisexual while a small minority is transgender, feeling as if they are one gender trapped in the body of the other gender. Sexual orientation and gender identity are not a choice and appear to be established by early childhood. They likely are shaped by both biological and environmental influences. Pediatrics now regards homosexuality and bisexuality as normal and healthy developmental outcomes. Transgenderism continues to be listed in the Diagnostic and Statistical Manual, 4th edition (DSM-IV) under the designation "Gender Identity Disorder," although the appropriateness of this continues to be debated. It is important to recognize that there are significant risks to growing up lesbian, gay, bisexual or transgender (LGBT) in American society. Certain segments of society regard a minority sexual orientation or transgender identity as pathologic or sinful. Many LGBT youth experience violence at school and in their own homes. Growing up with a stigmatized identity, or forced to hide one of the most important part of who they are, LGBT adolescents often encounter problems at home, at school, and in their communities. A small percentage run away from home, drop out of school, and turn to drugs, street-life, prostitution, or suicide as a means of escape. A larger percentage choose to postpone their sexual development or lead secret sexual lives that distort their sexual development and place them at high risk for depression, exploitation, violence, HIV/AIDS, and other sexually transmitted infections. Health providers have a special responsibility to these disenfranchised youths to make sure that they have access to accurate information, appropriate health care, and supportive community services so they may develop into healthy and productive adults. It is important to note that the American Academy of Pediatrics has taken a strong stand against "reparative therapies' and "transformational ministries" that seek to change sexual orientation from homosexual to heterosexual. These interventions are regarded as harmful and unethical.

A health provider has multiple roles in addressing issues of sexuality with adolescent patients, including those of screener, educator, counselor, and advocate. Research indicates, however, that many providers feel uncomfortable and unskilled in discussing sexuality with their adolescent patients. Therefore, providers must first examine their own comfort and attitudes about sexuality, particularly as these relate to adolescents, and reflect on how these attitudes affect their work with teenagers.

In their role as screeners, health providers should monitor their patients' sexual development by routinely asking questions related to sexual feelings and behaviors, preferably well before the onset of sexual activity. As educators, providers are in an excellent position to provide accurate information and anticipatory guidance to teenagers and their families, not only about pubertal development but also about normative sexual development during the adolescent years. It is especially important that they inform teenagers and their families about pediatrics' position on such controversial issues as contraception, masturbation and sexual orientation. As counselor, the provider should encourage postponement of sexual activity with others until the adolescent has the physical, emotional and cognitive maturity to enter into relationships that are consensual and non-exploitative. The provider should counsel adolescent patients that healthy sexual relationships should be both honest and pleasurable, and that steps should be taken to prevent sexually transmitted infections and unintended pregnancy. At a community level, health providers are in an excellent position to participate in the development and delivery of comprehensive sexuality curricula in the schools and other community forums. They also can be strong advocates for the development of confidential, accessible and affordable reproductive services for teenagers and for policies that nurture and support the healthy sexual development of all adolescents.

Questions

1. True/False: The incidence of U.S. adolescent sexual activity has increased over the past decade.

2. A 16-year-old boy reveals to you that he has become increasingly aware of his sexual attraction to other boys. Which is the most appropriate first response as a pediatrician to this revelation?
   a. Reassure the boy that such feelings are normal and may or may not be indicative of a homosexual or bisexual orientation.
   b. Report this revelation to the patient's parents.
   c. Refer the patient to a therapist trained in "reparative therapy."
   d. Discuss the dangers of anal intercourse, including HIV infection and other STIs.
   e. Suggest the boy spend more time with appropriate male role models and activities.

3. True/False: The onset of sexual activity in older adolescents may have different antecedents, predictors and consequences than that in younger adolescents.

4. True/False: Sexual experimentation is a normal part of adolescent development.

5. In the field of pediatrics which of the following is considered abnormal in adolescent sexual development.
   a. Masturbation
   b. Sexual coercion
   c. Homosexual orientation
   d. Sexual fantasies
   e. Sexual experimentation

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Answers to questions

1. False. The incidence of adolescent sexual activity, at least among in-school youth, appears to be declining. In addition, sexually active adolescents report fewer sexual partners and are more likely to use condoms than teenagers in the early 1990s.

2. a. Same-sex attraction is considered a normal part of adolescent and adult sexual experience. It may or may not reflect a bisexual or homosexual orientation, either of which, like heterosexuality, is believed to be established in early childhood and represents a normal developmental outcome.

3. True. The onset of sexual activity in younger adolescents is more likely to be associated with a history of negative life experiences and high-risk behaviors such as sexual abuse, substance use, parent-teen conflict and school problems. In older adolescents, the onset of sexual activity is often a more normative process.

4. True. Pediatrics as a discipline recognizes that sexual experimentation, with oneself and others, is a normal part of adolescent development. More controversial are the issues of age of initiation of sexual activity and the nature of those activities. There is a wide spectrum of viewpoints within pediatrics, reflecting broader societal views, on these latter issues.

5. b. Sexual coercion is a form of violence and, therefore, pathologic. Masturbation, homosexual orientation, and sexual fantasies and experimentation are considered a part of the spectrum of normal adolescent sexual development.

Chapter XX.7. Adolescent Gynecology

Renee L. Sato, MD

This is a 14 year old female who is brought to the Teen Health Clinic by her mother with a chief complaint of "missed periods" for 2 months. She experienced menarche at age 13. She believes her menses have been "more or less" regular but she has never kept track. She cannot remember the exact date of her last menstrual period. She states that when she has her menses, she has pain that is occasionally bad enough that she misses school. Her mother reports that her daughter has not had a period in at least two months and she wants you to test her for pregnancy and screen her for any sexually transmitted diseases (STD). She vehemently denies any sexual activity. She states that she feels perfectly fine and refuses to have a pelvic exam performed.

PMH: Unremarkable. No history of bleeding disorders. No current medications.

FH: Mother experienced menarche at age 13. No FH of bleeding disorders, gynecological tumors or other gynecological problems.

ROS: Unremarkable

Exam: VS are normal. Height and weight are 75th percentile for age. She is a well developed, adolescent female, in no acute distress. Non-hirsute. HEENT exam is normal. You ask her mother to step outside for the pelvic exam. While she is outside, you continue your questioning. She admits that she is sexually active. She uses condoms "sometimes" but her boyfriend doesn't like them. She states that she couldn't possibly have an STD because her boyfriend is "not that kind of person." She asks if you could give her some type of birth control and keep the conversation a secret from her mother. You explain carefully the need for a thorough gynecological exam and how the exam will be done. After talking with you a while, she agrees to have the pelvic and STD screen. She declines an HIV test.

Breasts: Tanner stage 4. Pelvis: Pubic hair tanner stage 3. Genitalia: Normal outward appearance. No malodor or discharge at the introitus. No vesicles, ulcers, or other lesions. Speculum/Pelvic Exam: Normal-appearing, nulliparous cervix. A Pap smear is performed and cervical swabs are obtained. No cervical motion tenderness is present. Non-gravid sized uterus palpable, without masses. Bilateral ovaries non-enlarged. No adnexal tenderness. The rest of her exam is normal.

Labs: UCG (-), WBC 7.0, Hg 13.8, Hct 40%, Plt 200, serum iron 100ug/dL, ferritin 80 ng/mL, RPR (-). A wet mount and KOH test are negative for yeast infection, bacterial vaginosis, or trichomonas. The GC and chlamydia assays are negative.

Clinical Course: After discussing contraceptive options with the patient, she decides on the combined oral contraceptive pill. She is counseled on monitoring her menses. Before she leaves, you warn her about HIV and STDs, and encourage condom use.

One month later, you get a call from her mother who is upset when she sees her medical insurance statement which shows an itemized expense list which contains a pregnancy test, a gonorrhea culture, and a prescription claim for birth control pills. She demands an explanation.

When dealing with the adolescent patient, it is important to remember that the adolescent is the patient, even if she is accompanied by a parent, usually the mother. At this stage of development, many adolescents are struggling to assume an adult identity and the patient

may resent being talked about in her presence as though she wasn't there. She may have concerns that are different from an adult. An adolescent will likely be anxious about the gynecological exam. She may be afraid that it will be painful, and will likely be embarrassed about undressing (1). In allaying such fears, it would be helpful to direct the majority of the initial discussion toward the adolescent and to explain the exam completely. Speaking to the mother alone is useful for obtaining family history that may be pertinent and for uncovering any concerns that she may have. The patient may be suspicious of your private conversations with her mother. Often, the patient can be reassured by telling her what was discussed. Patients in this age range are often modest about the changes taking place in their bodies, and it is often best to leave it up to the girl whether she wants her mother present during the exam. It is important to speak to the patient alone at some point because she may have information that she is reluctant to reveal in the presence of her mother.

When attempting to solicit information about her menstrual cycles, it is best to ask specific questions regarding the frequency of menstrual flow, length of menses, and the amount of blood lost. Do not accept without question the patient's assurance that her periods are "normal" or "regular". When assessing the amount of blood lost, the patient should be asked how long it takes to soak through a tampon or pad, if she ever has to awaken in the night to change a pad, or if she has to use both methods at once. It is not enough to simply note how many pads or tampons the patient uses in a day because she may change pads as soon as one is soiled, wait until it is soaked, or change it according to her class schedule which dictates when she can make it to the restroom.

Menarche is the onset of menstruation in girls. As the hypothalamic-pituitary-gonadal (HPG) axis matures during puberty, the hypothalamus begins pulsatile secretion of gonadotropin releasing hormone (GnRH). GnRH stimulates the pulsatile secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary, approximately every 90-120 minutes. In turn, LH stimulates the theca cells of the ovary to secrete androstenedione, testosterone, and estradiol. FSH increases the number of granulosa cells in the ovarian follicle and promotes the conversion of androstenedione to estradiol in the granulosa cells. Estradiol promotes the formation of uterine endometrial glandular cells and stroma. Menarche occurs when estrogen levels are sufficient to stimulate proliferation of the uterine endometrium. Estradiol also stimulates the development of the follicle and its levels increase in puberty until ovulatory cycles are established. The rising estradiol levels positively feedback to stimulate an LH surge, prompting ovulation. Following menarche, plasma estradiol levels range from 50-200 pg/ml during the follicular phase, while progesterone levels range from 200-2500 ng/dl (average 750) during the luteal phase (2).

Menarche in North American girls occurs at a mean age of 12.7 years, with a range of 10-16 years, and occurs an average of 2 years after the onset of breast development (2,3). The majority of cycles within the first 2 years after menarche are anovulatory, and there tends to be great variance in cycle interval, duration of flow, and amount of blood loss. Cycle intervals may be as long as 6 months and continue to be irregular for the first 15 cycles (2,4,5,6).

Dysfunctional Uterine Bleeding

In a normal cycle, an average of approximately 35 mL blood is lost (range 20-60 mL) (7). The amount of blood loss is difficult to estimate by sight. A good guideline may be to consider 8 pads or 12 tampons, well soaked, as the upper limit of normal; however even these estimates are user-dependent and may not correlate well with actual blood loss. The normal duration of flow is 3-7 days, with >7 days considered prolonged. A normal cycle interval ranges from 21-35 days, with less than 21 or more than 35 days considered abnormal (8).

Until ovulatory cycles are established in the adolescent, endometrial proliferation occurs without progesterone regulation. The endometrium grows until the level of estrogen cannot sustain it, resulting in endometrial sloughing. In the adolescent, this results in cycles that are irregularly regular until regular ovulation is established. Although cycle lengths will vary, they tend to stay within the normal range. The time to develop ovulatory cycles is dependent on the age at which menarche occurs. When the ages of menarche were <12.0 years, 12.0-12.9, and 13.0 years or greater, it took, respectively, 1, 3, and 4.5 years to attain 50% ovulatory cycles (9). The same study demonstrated that it may take 6-7 years to attain 90% or greater ovulatory cycles. Most importantly, although most menstrual cycles in early adolescence are anovulatory, truly abnormal bleeding is rare.

Classification of Abnormal Uterine Bleeding in the adolescent (8):

Menorrhagia (hypermenorrhea): Prolonged (more than 7 days) or excessive (>80 ml) of uterine bleeding occurring at regular intervals.

Polymenorrhea: Regular episodes of uterine bleeding occurring at intervals of <21 days.

Metrorrhagia: Uterine bleeding occurring at irregular intervals with variable amount of flow.

Menometrorrhagia: Irregular and frequent bleeding, which may be excessive in amount and/or prolonged in duration.

Oligomenorrhea: Irregular bleeding episodes occurring at intervals of 35 days to 6 months.

Amenorrhea: No menses for at least 6 months.

Intermenstrual bleeding: Bleeding episodes occurring between regular menstrual periods.

Postcoital bleeding: Bleeding occurring after sexual intercourse.

Hypomenorrhea: Decreased amount of uterine bleeding occurring at regular intervals.

Dysfunctional uterine bleeding: Excessive uterine bleeding with no demonstrable organic cause.

The most common cause of excess irregular bleeding in the adolescent is dysfunctional uterine bleeding (DUB), comprising 50% to 97% of causes (10,11,12). The most common etiology of DUB is anovulatory cycles, but this can only be diagnosed after all organic causes have been ruled out. Included in the differential for an adolescent who presents with excessive uterine bleeding are: Pregnancy, spontaneous abortion, trauma, foreign bodies in the vagina, complications of contraceptive devices or hormones, infection, coagulation defects, platelet abnormalities, leukemia, drugs or medications, polycystic ovary disease, or endocrine disorders such as hypo/hyperthyroidism, Addison's or Cushing's disease. Although polyps, myomas, tumors, or endometriosis may be included in the differential, in contrast to the mature woman, diseases of the uterus are rarely the cause for irregular uterine bleeding in adolescents (10,11,12).

A common clinical problem seen by physicians is the adolescent who presents with irregular intervals of bleeding that is normal in duration and amount of flow. For most of these adolescents, reassurance and observation are usually sufficient. The adolescent should be encouraged to keep a record of duration of menses, cycle interval, and amount of bleeding. Bleeding that is outside of normal parameters requires further evaluation (13). Signs of chronic disease, polycystic ovary disease, endocrine abnormalities, or blood dyscrasias, if present, should be evident in the physical exam with corresponding symptoms obtained in the history. The evaluation of abnormal uterine bleeding in the adolescent also requires a thorough gynecological exam. If the bleeding is active, the site of bleeding should be

determined, as occasionally rectal or urethral bleeding may be mistaken for menstrual spotting. A speculum exam should be performed to inspect for signs of infection, trauma, foreign bodies, or evidence of contraceptive devices. Cervical cultures, a wet mount, and a Pap smear are obtained as necessary. Vaginal irrigation may be used to obtain these samples in the patient who will not tolerate a speculum exam. A bimanual pelvic exam is used to check for cervical motion tenderness, adnexal tenderness, and masses. A single-finger digital palpation is adequate for most adolescents, but if the hymenal orifice is still too small for a single-digit exam, a rectoabdominal bimanual palpation may be done instead. Initial laboratory evaluation should include a CBC, coagulation studies, serum iron and ferritin, and urine or blood HCG. The following studies should be added if clinically indicated: thyroid studies, prolactin level, glucose, STD screen, hormone levels to evaluate for hirsutism or polycystic ovary disease (DHEAS, testosterone, 17-OH progesterone, LH, FSH). A pelvic ultrasound, endometrial biopsy, or pituitary CT may be added if warranted. Surgical interventions, such as a hysteroscopy and D&C are diagnostic methods of last resort (13).

After organic, systemic, and iatrogenic causes are ruled out, the abnormal bleeding may be diagnosed as dysfunctional uterine bleeding (8). Most adolescents with irregular bleeding in the first two years following menarche do not require long term management (10). If the bleeding interferes with the patient's daily activities or is severe enough to cause anemia, treatment is recommended. If anovulation is the suspected etiology, the initial hormonal intervention should be progestin therapy to initiate a secretory change of the endometrium and produce a controlled withdrawal bleed. Progestin stops endometrial growth and organizes endometrial sloughing so that menses will occur following progestin withdrawal, rather than at random times. Failure to bleed with progestin withdrawal warrants further workup. Estrogen treatment causes the regrowth of endometrium over raw, denuded areas where previous bleeding occurred. It is often clinically useful in controlling acute bleeding episodes, but progestin therapy is also required if the etiology of the bleed is anovulation. Combination estrogen/progestin oral contraceptives are the treatment of choice in adolescents, and also serve the dual benefit of preventing pregnancy if the adolescent is sexually active (8).

Dysmenorrhea

Dysmenorrhea is defined as cramping pain in the lower abdomen that occurs in conjunction with menstruation. If the pain is due to pelvic pathology or alterations in normal pelvic anatomy, the pain is classified as secondary dysmenorrhea, whereas primary dysmenorrhea occurs in the absence of any known pelvic pathology. Secondary dysmenorrhea is uncommon in adolescents, but primary dysmenorrhea is the most common gynecologic problem in young women, with reported rates as high as 75-90% (14,15,16). The incidence increases with sexual maturity, with one study reporting a 38% incidence at Tanner stage 3, increasing to 66% at Tanner stage 5. Dysmenorrhea also increases with chronological age from 39% in 12 year olds to 72% in 17 year olds. 14% of girls in one study frequently missed school because of menstrual pain, and of those with severe dysmenorrhea, 50% reported missing school (17).

Symptoms of primary dysmenorrhea are usually noted beginning 1-3 years after menarche. It is more commonly seen in girls who have established ovulatory cycles. Pain that begins within 6 months or 3 years after menarche is more indicative of secondary dysmenorrhea. Patients typically report intermittent, cramping suprapubic pain that may radiate to the lower back or thighs. The pain may begin a few days before menstruation and continue for as long as 7 days following the start of flow. More commonly, the pain begins a few hours after the start of menstruation, and lasts 24-48 hours. The pain is often accompanied by systemic symptoms including nausea and vomiting, fatigue, diarrhea, lightheadedness, and headaches. Often, there is a family history of dysmenorrhea, and the physical exam is completely normal (18).

Due to the nature of the symptoms and the timing of the pain coincident with menses, a focused history and physical exam is usually sufficient to rule out non-gynecologic conditions of lower abdominal pain such as appendicitis, urinary tract infections, or inflammatory bowel disease. Secondary causes of pelvic pain must be ruled out. As with all women of child-bearing age, pregnancy must be excluded, along with the possibility of ectopic pregnancy. Premenstrual syndrome (PMS) will also occur cyclically with menses, but is usually associated with breast tenderness and abdominal bloating rather than abdominal cramping. A history of infection or previous abortion or surgery may indicate pelvic inflammatory disease (PID) or adhesions from inflammation and scarring. Any sexually active adolescent should have a speculum exam with cultures taken for Chlamydia trachomatis and Neisseria gonorrhoeae, and have a Pap smear. A pelvic exam should detect any unusual masses, cervical motion tenderness typical of PID, or cervical stenosis. Secondary causes such as endometriosis, polyps, fibroids, or tumors are rare in adolescents, and a workup for these conditions are not usually indicated. In many instances, it is preferable to confirm the diagnosis through a therapeutic trial of NSAIDs (16).

Most of the symptoms of primary dysmenorrhea are now thought to be due to the effects of endogenous prostaglandins, particularly PGF2alpha. The secretory endometrium contains high levels of PGF2alpha which are released when the endometrium is sloughed off during menstruation. These prostaglandins stimulate uterine contractility and painful cramping. The levels of PGF2alpha are highest in the first two days of menses, when symptoms are most severe, and have been shown to be elevated in women who complain of severe dysmenorrhea (16). NSAIDs are the treatment of choice for initial therapy of dysmenorrhea in adolescents. These drugs act to inhibit prostaglandin synthetase, and have reported efficacy rates of 64-100%. In contrast, aspirin and acetaminophen were not shown to be superior to placebo in double-blind studies (19,20). Unfortunately, many adolescents self-treat for dysmenorrhea without consulting an adult. Of those that are self-treating, many take ineffective medications (aspirin or acetaminophen) or use less than the recommended dosages. Therefore, it is important for physicians to inquire about dysmenorrhea during routine visits to ensure that patients are being treated appropriately. Oral contraceptives are a second treatment option for dysmenorrhea that is highly effective (90%) and also serves the dual benefit of birth control for sexually active adolescents. For the roughly 10% of those who do not respond to these options, other alternatives exist ranging from laparoscopic surgery to acupuncture (16).

Contraception

By their 18th birthday, 56% of female adolescents have had intercourse (21). Each year, more than 1 million females 15-19 years old become pregnant, with the vast majority of these pregnancies unintended (22). An effective strategy to reduce unintended pregnancies and sexually transmitted diseases is to provide teens with basic information about reproduction and contraception (21). Contraceptive options for adolescents must be tailored to their specific needs and concerns. Factors to consider in choosing a contraceptive for an adolescent include: ease of use, STD protection, cost, safety, and acceptability.

Combined oral contraceptives (COC): AKA "The Pill". These consist of a daily tablet containing a combination estrogen and progestin taken continuously for 3 weeks, with one week of placebo pills to allow menses. COCs inhibit the midcycle gonadotropin surge, thereby preventing ovulation. They also thicken the cervical mucus, making passage of sperm into the reproductive tract more difficult, and thin the lining of the endometrium, making it less favorable for implantation. They have a perfect use failure rate of 0.1% with a typical failure rate of 3% even when an occasional pill is missed (23). COCs have multiple noncontraceptive benefits which are not

usually appreciated by adolescents, such as the reduction of endometrial and ovarian cancer. One benefit that many young women may appreciate is the recent FDA approval of one COC, OrthoTricyclen, for the treatment of acne. COCs may also be beneficial in young women who experience heavy, prolonged, or painful menses. This method does not require the cooperation of a partner, and does not interfere with spontaneity. Oral contraceptives, however, do not protect against STDs so teens should be encouraged to also use condoms. The patient must be motivated to take a pill every day in order for this method to be successful. Contraindications include: history of breast cancer, thromboembolic disease, pregnancy, undiagnosed abnormal uterine bleeding, smoking, heart disease or heart failure, CVA, or liver tumors. Older formulations of "The Pill" contributed to weight gain, but this is not seen with the newer pills on the market today. Teens who receive reassurance from their doctors that the new oral contraceptives will not cause them to gain weight are more likely to continue taking the pill long term (24).

Progestin only pill (POP): "Mini pill". This is a pill that is taken daily without any breaks. Its mechanism of action is similar to COCs. It thickens the cervical mucus and thins the endometrium to prevent implantation. Ovulation is suppressed only 60% of the time and the requirements for taking the POP are stricter. These pills must be taken at approximately the same time, every day. If a pill is delayed by more than 3 hours, the patient must be counseled to use a backup method of contraception for at least 48 hours. Perfect use failure rate is 0.5%, actual use 3-5%. POPs may cause irregular or breakthrough bleeding that may be stressful for the adolescent. In general, this method is not recommended as a first choice for most teens, but is useful for those with medical conditions where estrogen is contraindicated. It can also be used safely by nursing mothers (23).

DepoProvera: This is depot medroxyprogesterone acetate (DMPA) that is injected intramuscularly every 12 weeks. It works primarily by suppressing ovulation through a mechanism similar to the POPs. Its perfect use and actual use failure rate is 0.3%. Because the patient is required to return for a new injection every 12 weeks, it is still user-dependent, but the teen is freed from daily compliance worries. The major drawback of this method is that irregular bleeding or spotting has been reported in 25-50% of users in the first 6-12 months. However, most users eventually become amenorrheic. The patient should be properly counseled to expect these effects, and if she can get through the initial irregular bleeding, most teens find the lack of monthly menses appealing. This may be a disadvantage to those teens who rely on their periods as an indicator of pregnancy. This method is advantageous to certain handicapped adolescents and their caretakers. It provides both long-term birth control and the eventual freedom from messy menses (23).

Lunelle: This is a once-a-month injection of synthetic estrogen and progesterone (medroxyprogesterone acetate/estradiol cypionate). It provides the convenience of a once-monthly birth control method while minimizing the irregular bleeding that occurs with progestin-only contraceptives. The mechanism of action is similar to the COCs. The failure rate is currently estimated at 0.1 failures per 100 women-years. This method has only recently been approved for use. It requires that the patient return to their health care provider monthly for injections (25).

Ortho Evra, the first contraceptive patch, was introduced in 2002. It is placed on the skin of the buttocks, torso, or abdomen and releases a steady stream of estrogen and progestin (norelgestromin and ethinyl estradiol). A patch should be worn each week for 3 weeks in a row and changed every 7 days. The 4th week is patch-free to allow menses. The mechanism of action and side effect profile are similar to other hormonal contraceptives. Perfect use failure rate is 0.6%. The patch may be less effective in women >198 lbs compared to women with lower body weights. The risk of the patch falling off was <2% in clinical trials (26).

NuvaRing: The first hormonal vaginal contraceptive ring was approved by the FDA in 2001. NuvaRing is a small, flexible, transparent ring containing the hormones etonogestrel and ethinyl estradiol which are similar to the hormones in COCs. The ring is inserted into the vagina and provides a continuous low dose of estrogen and progestin for 3 weeks. It is removed in the fourth week to allow menses. A new ring is used each month. In clinical trials, pregnancy rates were 1-2% in one year of use. Side effects and contraindications are similar to COCs. Like all hormonal contraceptives, it does not protect against STDs or HIV (27).

Male latex condoms are the method of choice for adolescents, as they offer protection against both pregnancy and STDs. The male condom is the most common nonhormonal contraception used by adolescents aged 15-19 (28). Latex condoms have been shown to prevent the transmission of HIV, herpes, chlamydia, gonorrhea, cytomegalovirus, hepatitis B, trichomonas, and probably human papilloma virus (29). Perfect use failure rates range from 1-4%, with typical use failure rates of 10-21%. Teens should be instructed in the proper use of condoms. They should be advised to use spermicide, a water-based lubricant if needed, never a petroleum or oil based lubricant as these compromise the integrity of the condom, and to seek emergency contraception right away if the condom should break or slip. The most common deterrents to use are the interruption of intercourse required to put on the condom, the foresight required to purchase and keep the condom readily available, and the necessary cooperation of the male partner. Actual side effects, such as latex or spermicide allergies are not common (23).

Female condoms work as a barrier to sperm, similar to the male condom. It is a single-use, polyurethane pouch with a ring on one end that is inserted into the vagina to cover the cervix, and another open ring on the other end that remains outside the vagina. Perfect use failure rate is 3%, typical use failure is 15-25%. The advantages of this method are that it is the only female-controlled barrier method that offers protection against STDs comparable to the male condom, it is an alternative to females who have a latex allergy, and does not require male cooperation. Disadvantages include its higher cost ($3.00 per condom) and lesser availability, unusual appearance, and occasional crackling noise during intercourse or walking (23).

The diaphragm is a flexible rubber dome placed over the cervix and is used in conjunction with spermicidal jellies or foam. It may be inserted up to 6 hours prior to intercourse, but must be in place at least 30 minutes prior. It must be left in place for 6 hours after. The perfect use failure rate is 6% with a typical use failure of 20%. The diaphragm must be fitted by a physician and the patient must be able to insert and place it properly. It provides limited protection against some STDs but is not as effective as condoms. The initial cost of several hundred dollars may be discouraging to teens, but can be cost-saving in the long run if the patient is extremely active sexually. Disadvantages: Some teens are not comfortable touching their own genitals during insertion and removal. If positions are changed during sex, the diaphragm must be checked to make sure it is still in place. If the patient has a significant weight change, or becomes pregnant, she must be refitted. The diaphragm must be carefully inspected and cleaned between uses. There is a slight increase in urinary tract infections associated with diaphragm use, and if left in place >24 hours, there is a risk of toxic shock syndrome (23).

The contraceptive sponge was pulled off the market in 1995 for reasons unrelated to either safety or reliability, but it has become available again in 1999. The sponge is a doughnut-shaped polyurethane foam barrier containing a chemical spermicide. The sponge must be moistened with water and inserted into the vagina up to 24 hours prior to intercourse and may be left in place up to 30 hours. Perfect use failure rate is 10%. Typical use failure is 15-20% for nulliparous women, and has been reported as high as 40% in women who have had a child (30).

Spermicides come in a variety of forms (jellies, creams, foam, suppositories, tablets) that may be used alone or in conjunction with other methods. The most common active ingredients in spermicides are nonoxynol 9 or octoxynol, which acts to incapacitate sperm. In

addition, these spermicides may have some bactericidal action. Spermicides must be inserted vaginally 10-30 minutes prior to intercourse and a new application is required for each act of intercourse. The perfect use failure rate is 6% with a typical use failure of 25%. Spermicides are often perceived by adolescents as messy and inconvenient, and continuation rates are low (23).

Contraceptive methods that are not appropriate for adolescents include the cervical cap and intrauterine devices (IUD). Sterilization is not appropriate as it is considered a permanent end to fertility. (31)

Intrauterine devices (IUD) and cervical caps are not recommended for teens so they will not be discussed here.

Physicians should ensure that adolescents are informed of the availability of emergency contraception. Teens need to be made aware of this option ahead of time due to the narrow window of time that treatment can be effectively applied. It should be stressed that postcoital methods should not be relied upon as the primary birth control method, and are primarily intended for emergencies. The most common method is the prescription of a larger than normal dose of oral contraceptive pills usually within 72 hours of intercourse. Depending on the time of the cycle in which it is taken, emergency contraceptive pills may inhibit ovulation, interfere with fertilization, or inhibit implantation of a fertilized egg. They should not be confused with abortifacients such as RU486 which are designed to end established pregnancies.

In general, the male condom is the most appropriate birth control method for adolescents. It is readily available over the counter, inexpensive, and protects against both pregnancy and STDs. Adolescents should be encouraged to use condoms, but a second method may be appropriate if condom use is less than perfect. Hormonal methods do not offer protection against STDs, but have low failure rates. The most common side effect of progestin-only methods is irregular bleeding. Many adolescents are not comfortable touching their own genitals, making internal barrier methods such as the diaphragm, the sponge, or the cervical cap less than ideal methods for many teens.

STD screening

The gold standard for the diagnosis of Neisseria gonorrhoeae and Chlamydia trachomatis has been culture. Endocervical specimens for culture are typically obtained from swabs taken during a speculum exam, with additional pharyngeal and rectal swabs obtained as necessary. Culture for C. trachomatis has sensitivities of 60-80% and specificities close to 100% for endocervical specimens (32). Culture for N. gonorrhoeae is 58-96% sensitive (33). A single endocervical culture will detect 85% of N. gonorrhoeae infections. A second culture will catch an additional 7-10% of infections (34). Culture methods have several limitations. They are slow, generally requiring 3-7 days for results. Only viable organisms can be detected and test results can be affected by storage and transport conditions.

Recently, several alternative tests for the detection of chlamydia or gonorrhea have been made available with acceptable sensitivities and specificities. Newer DNA amplification tests increase diagnosis when used in conjunction with other detection methods, and can be performed on both endocervical specimens and urine samples. Urine based testing provides a unique method of noninvasive screening, and is especially helpful in young adolescents who may be uncooperative with the pelvic exam. Polymerase Chain Reaction (PCR) and Ligase Chain Reaction (LCR) are two DNA amplification methods used today. For the detection of C. trachomatis in endocervical specimens, PCR is comparable to culture (sensitivity 79-99% and specificity 99-100%). In urine samples, the measured sensitivity was 96-100% with a specificity of 99-100% (32). LCR results have outperformed culture (Endocervical: sens 94% and spec 100%); (Urine: sens 96% and spec 100%) (35). For the detection of N. gonorrhoeae, LCR has been proven equally sensitive to culture methods using both endocervical swabs and urine specimens. Most studies have shown a sensitivity of >88% and specificity of 99-100% for LCR (34,36). Another alternative to culture is the DNA Probe assay, which may be performed alone (unamplified) or in conjunction with DNA amplification. DNA amplification is recommended for all urine samples. The unamplified DNA probe has a sensitivity and specificity essentially equivalent to culture for endocervical specimens, but a sensitivity of only 50% in urine that has not undergone amplification (34,37). Enzyme Immunoassay (EIA) and Direct Fluorescent Antibody (DFA) were developed as an alternative to culture. Both these methods are faster than culture and can detect nonviable as well as viable organisms; however, their sensitivities have been shown to be variable with the prevalence of the disease. They are useful screening tools in populations where the prevalence of infection is high (32,34).

Questions

1. Can a physician provide family planning services to a minor without parental knowledge? If an adolescent demands confidentiality, how can a physician prevent the transfer of billing/insurance information to reach parents?
2. What is the normal age range for menarche?
3. What are some common treatments for dysmenorrhea?
4. Name some things that should be discussed with a female adolescent during a physician visit?
5. What is the normal cycle length, amount of blood loss, and duration of flow in menses?
6. What is the most common side effect of progestin-only contraceptive methods?
7. If a speculum exam cannot be performed, or the patient refuses, how can screening for chlamydia and/or gonorrhea be accomplished?

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Answers to questions

1. In Hawaii, a minor who is at least 14 years of age may consent to receive contraceptive services, prenatal care, and STD/HIV/AIDS services. The physician may notify parents (with the consent of the patient), but parental consent or notification is not required. In fact, if an adolescent demands confidentiality, it becomes a difficult situation since it might not permissible for the physician to release information, even to parents. The wording of the statute is, "left up to the treating physician's discretion in consultation with the minor who received medical treatment", but the statute later states that the minor, "shall have the same legal capacity to act" as an adult, making their demand for confidentiality no different than that of an adult. Most insurance companies provide itemized claim information to the subscriber of the insurance policy (usually the parent). It is not possible to circumvent this in most instances. Thus, adolescents should be counseled that once they have used their parent's medical insurance, their parents will receive such information. They must consent to this release of information, or they must remove the medical insurance information so that an insurance claim is not submitted. They should also understand that they will receive a bill for all medical services, although their ability to pay it should not impede the delivery of medical services. In most instances, it may be appropriate to counsel the adolescent to share this information with their parents, and in many instances, they will consent once they understand all the issues. This requires provision of factual information to the adolescent and patience.
2. 10 to 16 year old, average 12.7.
3. NSAIDs are the treatment of choice in adolescents. Oral contraceptives may also be used.
4. Adolescents should be provided with information about their diagnosis, contraception, breast self-exam, STDs and AIDS. Instruction should be provided on how to track menses. Condom use should be encouraged in those who are sexually active.
5. 21-35 days between menses, 20-60 mL blood loss (avg 35 mL), 3-7 days of menstruation.
6. Irregular bleeding.
7. PCR or LCR (DNA methods) for chlamydia and gonorrhea assayed from a urine sample or vaginal fluid sample.

Chapter XXI.1. Eczematous Dermatitis (Atopic Dermatitis and Seborrhea)

M. Stanton Michels, MD

This is a 2 year old toddler who has had "bad skin" since soon after he was born. He had "cradle cap" as an infant that became generalized to his face, and from there to his upper torso. Off and on throughout his life, he has had "flare-ups" of erythematous, scaling patches on his cheeks, chest and abdomen. His mother expresses frustration with the doctors' inability to help her son's skin. She has used moisturizers and 1% hydrocortisone cream episodically in the past. Presently his hands are so inflamed, cracked and bleeding that he doesn't move his fingers much. "He never stops scratching!", she declares. She admits however that they are more successful in controlling his asthma that was diagnosed about one year ago.

Atopic dermatitis (AD) largely starts in infancy and early childhood. 85% of cases first present before the fifth birthday. Common manifestations can include pruritus (which is universal), lichenification and linear cracking in those flexural areas, xerosis (dry flakey skin generally prior to the patchy outbreaks), periauricular fissures, cheilitis (inflammation and cracking of lips, particularly at the corners of the mouth), scalp dermatitis (e.g., cradle cap), and susceptibility to cutaneous infections by S. aureus.

Epidemiologically, atopic dermatitis seems to be increasing worldwide. Exact figures are lacking; however since there is not a strict method of defining the disease. There does seem to be some variation in rates from one ethnic or geographic area to another. Reported rates can run from greater than 20% in Scandinavian populations to less than 5% in east Africa.

Some would offer the diagnostic criteria of: itchy skin (mandatory for the diagnosis) plus at least 3 of the following:

1) Involvement of the skin creases.
2) Past medical history of asthma or hay fever.
3) History of generally dry skin.
4) Onset less than age 2 years.
5) Visible flexural dermatitis.

Other objective tests useful in the diagnosis might include total IgG and increased IgE. Genetics seems to play an important factor. Co-twin studies have shown a high concordance for the disease in identical twins over dizygotic twins. In addition, there is a strong relationship between atopic dermatitis and other allergic disease manifestations such as asthma and allergic rhinitis. AD characteristically displays two immune responses: 1) IgE overproduction, and 2) diminished cell mediated immunity. Cytokines, particularly IL-4 produced by T cells, seem to promote IgE production. It is hypothesized that an overwhelming T-cell activity which produces this aberrant lymphokine profile limits cellular immune response. This in turn may increase susceptibility to certain microorganisms. Interestingly, house dust mite, cat dander, and certain pollens have been related to atopic dermatitis exacerbations.

The question of food allergy is often posed by parents, but the connection to food allergies is less clear. The consensus is that food can play a role in certain individuals. Finding the specific food precipitant, however, is usually a time consuming and frustrating process. Although the literature is somewhat conflicting, it is generally held that less than 10% of AD children can be shown to have a specific food as a cause for their dermatitis. Skin testing or RAST blood tests are often not helpful in the diagnosis. Having said this, the most common offending agents, when one is identified, are eggs, milk, seafood, nuts, wheat, and soy. Elimination diets may not in the end alter the natural course of atopic dermatitis. Eczematous reactions may not become apparent until several days after the ingestion.

Differential diagnosis largely depends on the age and distribution of the rash. Although there is some dispute on the nomenclature, many authors would lump atopic dermatitis and seborrhea together in a group of eczematoid dermatitis. They stress that atopic dermatitis often occurs in individuals who had seborrheic dermatitis in infancy. There are some differences however. In early infancy, seborrheic dermatitis usually presents earlier than 2 months of age with AD presenting thereafter. Seborrhea has a much better prognosis, and usually resolves by six months of age, just when atopic dermatitis becomes more prevalent. Pruritus is not customarily a big factor in seborrhea, but is always present in AD. There are patches of erythema which usually start on the scalp and move down over the face and cheeks. These red patches scale and have an oily appearance. The rash itself is difficult to distinguish morphologically from atopic dermatitis. In older children, scabies can cause discrete areas of pruritus with papular erythema, but usually these show a predilection for the hands, feet, and genital areas. One will often find the tiny burrow wounds on close inspection (often in the web spaces between the fingers). Allergic contact dermatitis is more sudden in onset and less relapsing in course. Usually a specific new allergen can be identified by history. Very specific distribution is often helpful.

There are several more severe immune disorders that may be entertained. Hyper IgE syndrome (Job's syndrome) often produces more severe infections of tissues other than the skin, such as pneumonias, sinusitis, or deep soft tissue abscesses. Wiskott-Aldrich syndrome can produce flexural dermatitis which appears clinically as AD, and X-linked Bruton's agammaglobulinemia can also produce similar rashes, but shows low IgE levels. Histiocytosis-X can also present with patchy erythematous, pruritic rash.

As is the case with acne, the level of therapy should be tailored to the severity of the disease. Generally, AD patients are found to have dry skin, which may produce cracking that contributes to antigen stimulation of the deeper tissues. Without a doubt, moisturizers hold a key role in providing a barrier to this drying. Emollients are best, but a very greasy product may not be well tolerated by older patients although they form the best barrier. Systemic antihistamines may help with pruritus, and the more sedating of these, such as hydroxyzine, seem to have the greatest effect, particularly in younger children to avoid bed time scratching.

Corticosteroids form the main line of therapy. These should be started with 1% hydrocortisone, which is the mildest of the group. For more resistant cases, one will probably have to use fluorinated, high potency steroid preparations. Triamcinolone cream 0.1% can be used for flare ups. Very occasionally, particularly severe, body wide exacerbations, may require short bursts of systemic steroids (1-3 mg/kg per day of oral prednisolone), which is often successful in improving the severe exacerbation within a few days. There is a concern of systemic absorption of topical steroids, but many studies have failed to show an actual adverse effect unless there was long term use. However, potent topical corticosteroids, if used repeatedly or over long term, can cause skin thinning and striae. Should these measures fail, some have used tar or ichthammol. PUVA (psoralen + ultraviolet A light) enhances the absorption of UV-A selectively into the affected skin lesions. Cyclosporin has also been used.

Newer medications called non-steroid immunomodulators, tacrolimus (Protopic) and pimecrolimus (Elidel), are approved by the FDA (since 2000) for atopic dermatitis. Unlike corticosteroids, these can be safely used for long periods of time without the corticosteroid side effects of skin thinning and telangiectasia.

Seborrheic dermatitis is usually managed somewhat differently than AD. There is an overproduction of oil on the scalp which combines with superficial exfoliated cells of epidermis to form the scales that are so prevalent. Oils therefore tend to worsen this condition so that moisturizers are actually contraindicated. Indeed, when parents, thinking that the scales indicate dry skin, rub oil into the scalp of their baby, the condition usually worsens. Parents should be instructed to shampoo the scalp with mild baby shampoo and gently try to remove the flakes and scales with their fingers. When the condition creeps down onto the face, however, mild corticosteroid creams can provide great relief as is the case with atopic dermatitis.

Questions

1. True/False: Seborrhea starts in infancy at the same time as atopic dermatitis.

2. True/False: Many infants who have seborrhea will eventually develop atopic dermatitis.

3. True/False: The prevalence of atopic dermatitis is generally higher in more developed societies and may be in part related to diverse environmental stimuli present in these communities.

4. Which of the following is a true statement?
    a. Seborrhea produces dry scales on the scalp of infants.
    b. Both seborrhea and atopic dermatitis benefit from scale removal.
    c. Seborrhea is not pruritic.
    d. Hydrocortisone cream can be used in cradle cap dermatitis.

5. A 5 year old child presents with a red, itchy rash in a 2 cm band across his abdomen below the umbilicus. The most likely diagnosis is:
    a. Contact dermatitis
    b. Scabies
    c. Atopic dermatitis
    d. Shingles

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Answers to questions
1.False, 2.True, 3.True, 4.c, 5.a

Chapter XXI.2. Acne
M. Stanton Michels, MD

A 16 year old male presents for a pre-sports physical. His sole complaint is his acne, which he admits, has made him reluctant to ask female classmates out on dates. As his acne has become worse in recent years, he feels that he is becoming more withdrawn and self-conscious. He has tried Clearasil as an OTC medication, but he usually just "pops" the lesions when they appear. He'd like anything that would improve his complexion.

His exam is unremarkable except for moderately severe facial acne with secondary scarring.

Acne is a common skin condition of adolescent males and females. It is estimated that it affects 40% of teenagers at some point. The lesions take several forms:

Comedones come in two types. Closed comedones, also known as "whiteheads" are dilated plugged follicles that have not yet reached the surface. Often they are difficult to see and are 1-2 mm papules. When these reach the surface, the follicle becomes dilated at the orifice and are more visible as open comedones, or "blackheads

Inflammatory lesions that grow from comedones are of two types as well. Pustules are superficial, raised white lesions that are filled with pus. Pustules usually resolve in a matter of days without scar formation. Papules are deeper, dermal inflammatory lesions that are more erythematous, raised and solid. They take a longer time to heal and often result in scaring.

Cysts or nodules are the most severe form of acne lesions. These are really suppurative abscesses. Scarring is to be expected.

Scars take two forms. Ice pick scars are atrophic, broad-based depressions that reflect scarring of the deeper dermal tissues. Hypertrophic or keloidal scars are raised, thick fibrotic plaques that occur more frequently on the chest or shoulders. African-Americans are particularly prone to this form of scarring.

The pathogenesis of acne involves abnormalities in follicular keratinization with the excessive proliferation of Propionibacterium acnes. The excessive keratin produces a horny impaction or microcomedo. As this extends to the surface a comedone is formed. The sebaceous gland hypertrophies and secretes excess sebum. This process is greatly promoted by androgen hormones, and thus becomes most evident in puberty. Dehydroepiandrosterone (DHEA), from the adrenal glands along with testosterone, which is converted in the sebaceous glands to the more active dihydrotestosterone, are important in comedone formation.

P. acnes, which is an anaerobic diphtheroid, colonizes the impacted gland. Interestingly, the number of P. acnes bacteria on the skin surface do not correlate to the severity of the acne. Staphylococcus epidermidis and Pityrosporum ovale also are sometimes found from culture of the follicular material. P. acnes possesses a lipase that can hydrolyze sebum to free fatty acids. Intrafollicular free fatty acids promote inflammatory responses with chemotaxis of polymorphonuclear leukocytes and monocytes.

Therapy in acne is usually staged and relates to:

1. The type of lesion.
2. The acne severity.
3. The psychological impact of the disease.

Mild acne can usually be handled with a topical preparation antimicrobial such as benzoyl peroxide. This agent is bactericidal for P. acnes and comes in various strengths from 2.5 to 10% preparations. Higher concentrations are often used with truncal involvement.

Topical antibiotics are also useful in relatively mild cases of acne. Options here include erythromycin and clindamycin. Both have been shown to be equally effective although there are increasing reports of resistance to erythromycin. Pseudomembranous colitis secondary to topical clindamycin is almost unheard of.

For patients with more severe or inflammatory lesions, or those who failed to respond to topical therapy, systemic antibiotics are often added. These drugs can also have an anti-inflammatory effect and may decrease the chances of scar formation in patients predisposed to scarring. Options here include tetracycline BID or doxycycline once a day dosing. Of course these drugs should never be given to pregnant women or children under the age of 12 because of skeletal growth inhibition and discoloration of the teeth. Photosensitivity can also occur.

Topical Retin-A (tretinoin) and Differin (adapalene) normalize follicular keratinization by increasing turnover of cells lining the sebaceous gland. This invariably leads to irritation, erythema and desquamation of the skin that many patients find intolerable. The patient must be counseled prior to treatment about these effects and encouraged to give the drug a 3 month trial before deciding against its use.

Since hormones play a role in the pathogenesis of acne, hormonal manipulation is sometimes useful. The goal here is to reduce androgen production or inhibit androgen metabolism at the follicular level. Estrogen can be added to female patients in the form of oral contraceptives. This is unacceptable in male patients, due to the feminizing side effects. In a similar way, this option should not be used in patients younger than 16 years because of its adverse effect on growth in height.

Finally, systemic (oral) isotretinoin (Accutane) approaches the problem of comedone formation by decreasing sebum secretion. This depletes follicular P. acnes concentrations and then neutrophil chemotaxis. Hyperkeratosis is diminished. Accutane is an oral systemic analog of vitamin A and is indicated in patients with the most severe nodular or cystic forms of acne that have the highest propensity towards scar formation. Side effects are similar to hypervitaminosis A syndrome and include mucocutaneous inflammation, cheilitis (inflammation affecting the lips), conjunctivitis, and xerosis (eye dryness). Patients commonly complain of symptoms such as pruritus, chapped lips, and dry eyes. Moisturizing creams my help the cutaneous symptoms. Pseudotumor cerebri can also result which mandates stopping the drug. 25% of patients show an elevation of serum triglycerides, often with a rise in low-density lipoprotein levels. Liver enzymes may be elevated. The best-known side effect however is teratogenicity which has been shown to cause severe malformations in CNS, cardiac and craniofacial development. All female patients administered this drug should have a negative pregnancy test and advised not to become pregnant while taking the drug.

Questions

1. Organisms associated with the inflammatory process of acne include all of the following except:
    a. Pityrosporum ovale
    b. Propionibacterium acnes
    c. Strep pyogenes
    d. Staphylococcus epidermidis

2. All of the following are true statements are true of isotretinoin except:
    a. Cheilitis and xerosis necessitate discontinuing the drug
    b. Pseudotumor cerebri is sometimes irreversible
    c. The drug can be used in fertile women
    d. Increased levels of low density lipoproteins are sometimes seen

3. True/False: Comedones can be thought of as small pustules that can eventually develop into cystic acne.

4. True/False: Closed comedones are composed of small pus collections.

5. True/False: Retin-A (tretinoin) and Accutane (isotretinoin) both act to decrease hyperkeratosis.

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Answers to questions
1.c, 2.a, 3.False, 4.False, 5.True

Chapter XXI.3. Hemangiomas, Vascular Malformations and Nevi

M. Stanton Michels, MD

A 12 month female is brought in by her mother because she afraid that her daughter has a skin tumor. What started as a small red spot on her cheek has recently grown to almost the size of a dime. It now "sticks out" and can be palpated with a bulging appearance. Mom is also concerned because other people have remarked about the lesion, but the child seems unconcerned as it seems to cause no pain.

The child's exam is normal except for a 1 cm bright red strawberry colored mass on her cheek which is elevated approximately 4 mm higher than the surface of her skin. You advise her parents that this is a strawberry hemangioma which should resolve on its own. Surgical removal is not advised since this will result in more scarring than letting it involute on its own.

Various methods of categorizing congenital vascular lesions have arisen. One common grouping is to separate these entities into: 1) Hemangiomas, sometimes termed vascular nevi, and 2) Vascular Malformations.

Hemangiomas are defined as benign neoplasms with proliferating vascular endothelium. This endothelium enlarges, stabilizes, and finally undergoes involution. Vascular malformations on the other hand, are hamartomas of mature endothelium that do not proliferate. Hemangiomas are also more common in females with at 3:1 or even 5:1 ratio. This may be related to the common finding of high levels of estrogen receptors in the proliferating lesions. Hemangiomas are usually single lesions, but multiple lesions occur in less than 25% of cases. If one measures H-thymidine uptake in these lesions, one finds increased proliferation. Another interesting feature is the number of mast cells in these lesions on microscopy is up to 10 times the number in otherwise normal tissue.

There are well-defined stages of hemangiomas: proliferate, stationary, and involutional phases. Characteristically the lesions grow and become more protuberant over a period of time and adopt the typical raised configuration of the "strawberry" hemangioma. Then they slowly regress and in about 75% of cases, they completely disappear by age 7 years. Overall spontaneous resolution occurs in greater than 90%. Treatment is usually discouraged because a variety of techniques including surgery, cryotherapy, laser therapy, injection of sclerosing agents, and photocoagulation have all caused scarring that is unacceptable compared to the typical spontaneous resolution.

One particular type of hemangioma should be mentioned, Kasabach-Merritt syndrome. In this condition, the hemangioma is very large and extends to deep structures. Complications can include disfigurement; high output cardiac failure, infection and thrombocytopenia with acute or chronic consumptive coagulopathy as in DIC.

Vascular malformations make up about two thirds of all lesions in the newborn. Common vascular malformations include the "salmon patch" which are extremely common and usually fade spontaneously, and the "port wine stain" or nevus flammeus, which is permanent. Port wine stains occur in 0.3% to 0.6% of children. When this occurs on the posterior neck, it is termed the "stork bite", or on the eyelids, the "angel's kiss". Most of the lesions on the face fade with time. Some of the occipital patches persist.

Unlike the hemangioma group, the port wine stains are composed of mature capillaries that are limited to the dermis alone. As the number of vessels increases and age, the color can change from bright pink to dark purple. As facial port wine stains age, the vessels undergo progressive ectasia, developing a dark violet hue and often a roughening skin texture. The can lead to considerable emotional impact on the part of the child and the parents as well. Laser treatment is available for this condition. Certain parts of the skin act as targets that absorb specific wavelengths of light. The light is converted to heat, which destroys the target. Careful selection of the wavelength administered can direct precise treatment with minimal peripheral destruction. This tends to decrease scaring, although some degree of scar formation is always possible.

There are several syndromes that can be associated with vascular malformations. The most common of these is Sturge-Weber Syndrome. Externally, this presents with a port wine stain over areas of the face innervated by the first division of the trigeminal nerve (V1). The significant hidden finding is the ipsilateral leptomeningeal angiomatosis. Classically this produces railroad track calcifications of cortical vessels seen on plain skull films. CT may show these cortical calcifications earlier in life than routine X-ray. Other concomitant findings include seizures in 55-97%, mental retardation and various eye findings including glaucoma, visual defects, optic atrophy, cataracts, retinal detachment and heterochromia of the iris. For this reason, CT is advised for the infant with a port wine stain in the first division of the trigeminal nerve distribution. Serial ophthalmologic examination is necessary to screen for glaucoma.

Nevi are collections of normal melanocytes. The lay public terms these moles. The greatest concern about them comes from the fact that some undergo malignant transformation to melanoma. Nevi fall into several classes.

Giant congenital nevi are defined as being greater than 20 cm in diameter. 6% of these will turn malignant within the individual's lifetime. Therefore, most authorities feel that they should be removed if at all possible. Sometimes the location or extent makes removal very difficult. Some practitioners advocate the removal of all congenital nevi, regardless of size because of this theoretic danger.

Acquired melanocytic nevi, or common moles can appear at any time after birth. They are often divided into 3 common types: 1) Junctional nevi have melanocytes that are limited to the epidermis. 2) Compound nevi have nevus cells both at the dermal-epidermal junction and lower inside the dermis. They frequently are raised but smooth bordered. 3.) Intradermal nevi have nevus cells completely within the dermis. These are raised, dome shaped, and smooth bordered. There is the theoretic possibility of malignant transformation in these nevi as well, but the rate is so low that these nevi do not need to be removed.

Lentigines are small, (less than 1 cm), hyperpigmented macules which unlike freckles, can develop on sun exposed skin but also on unexposed areas of the body. Several syndromes may be associated with lentigines. The most well known of these is Peutz-Jeghers syndrome. This entity also includes characteristic pigmented lesions on the lips and oral cavity. It is dominantly inherited, but what is most problematic is the associated intestinal polyps which may cause cramping or bleeding.

Café au lait spots are another type light brown hyperpigmented lesions, which if more than 5 or 6 in number can herald neurofibromatosis or von Recklinghausen's disease.

Questions

1. True/False: Proliferating vascular endothelium can be arrested with laser treatment.

2. True/False: The concerned parent whose child has a protuberant, growing vascular lesion in early childhood can often be reassured that the lesion will involute with time.

3. Common manifestations of Sturge-Webber Syndrome include all of the following except:
   a. Meningeal vascular malformations
   b. Choanal atresia
   c. Homonymous hemianopia
   d. Mental retardation

4. True/False: Like most hemangiomas, Kasabach-Merritt Syndrome lesions tend to involute with time, but do not disappear.

5. True/False: Lentigines are "age spots" that crop up in sun exposed areas.

6. True/False: Peutz-Jeghers syndrome often is picked up when hyperpigmented macules are found on the lips of children with chronic abdominal pain.

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Answers to questions

1.False, 2.True, 3.b, 4.False, 5.False, 6.True

Chapter XXI.4. Burns
Annemarie Uliasz

This is a 3 year old male who is brought to the emergency room after suffering burns to the right arm when a hot cup of coffee spilled on him. His family applied gel from an Aloe plant to the burn before coming to the ER. He is otherwise healthy and his immunizations are up to date.

Exam: VS T 37.5, P120, R20, BP (unobtainable, crying), oxygen saturation 100% in room air. Weight 15 kg. He is alert and active, in moderate distress. His right forearm appears mostly red, and is painful upon palpation. Blanching is apparent on palpation. One smaller intact blister and one large ruptured blister are present on the dorsal aspect of the right forearm. The blistered surface area is estimated to be 2% and the non-blistered red area is estimated to be 2% for a total body surface area (TBSA) of 4%.

The physician recommends an IM dose of morphine, but his parents decline this, so acetaminophen with codeine is given instead. Cool, sterile, saline-soaked gauze is applied to the wound surface and the open areas are gently cleansed with saline. Tissue from the ruptured blister is removed and the intact blister is flimsy so it is drained and removed. Silver sulfadiazine cream is applied to areas of partial thickness burns and the burns are dressed. He is discharged with instructions for the parents to gently cleanse the burns with mild soap and water, reapply the antibacterial cream, and change the dressing each day. His burn healed completely without complications in five weeks.

Fires are second only to motor vehicle crashes as a leading cause of death in children. In the US, approximately 1.2 million people seek medical treatment for burns. Approximately 50,000 are hospitalized. One third to one half of these are under 18 years old. Children from birth to age 4 account for nearly 50% of all pediatric burns (1). After age 4, the incidence of burn injuries declines only to rise again in adolescence as individuals enter the work force.

Skin is the largest organ in the body. It consists of three main layers: the epidermis, the dermis, and the subcutaneous tissue. The epidermis is the outermost layer of the skin. It is composed of viable cells that mature and differentiate into cornified cells as they reach the skin surface. The superficial layer of anuclear cornified cells is called the stratum corneum. The stratum corneum prevents water and electrolyte loss, as well as acting as barrier to the entrance of microorganisms.

Deep to the epidermis is the dermis. The dermis is made up of stroma, a dense fibroelastic connective tissue containing collagen and elastic fibers, and ground substance, an extracellular gel. The dermis contains an extensive neurovascular network, special glands and appendages that communicate with overlying epidermis. The innermost layer of skin is subcutaneous tissue. It consists of fatty connective tissue, skin appendages, glands, and hair follicles.

Burns are classified according to the depth of injury. First degree burns are limited to the epidermis. A sunburn is an example of a first degree burn. These burns are red, dry and painful with no epidermal sloughing or blistering. Blanching is visible when pressure is applied to the wound. First degree burns do not lead to scarring, and require only local wound care. Second degree (partial thickness) burns extend into the dermis, with some residual dermis remaining viable. These burns are pink to pale pink, moist, and painful. They blanch on application of pressure. Epidermal sloughing and blisters are present. In third degree (full thickness) burns, the entire dermis is destroyed leaving subcutaneous tissue exposed. These burns appear white, mottled, or charred. They are dry and may be firm or leathery. Third degree burns do not blanch and are not painful. Fourth degree (transmural) burns extend through the subcutaneous tissue, exposing muscle and bone. They are usually associated with a lethal injury.

Most pediatric burn injuries occur at home and are largely preventable. In children younger than 4 years old, the most frequent burns are scalds. These injuries are the result of exposure to hot liquids (pulling pots off the stove, spilling hot beverages, or hot tap water). The second most frequent cause of burn injuries is contact with hot objects (the stovetop, a hot oven door, clothes irons, or curling irons). Furthermore, infants, toddlers, and small children may not be able to escape the burning object as well as an older child. Prolonged duration of contact may increase the severity of the injury. In older children, the majority of burns are due to fires and environmental causes such as hot barbecue grills, hot mufflers or engines.

Although the majority of pediatric burns are accidental, approximately 20% of burn injuries occur as a result of child abuse (2). If a non-accidental burn is suspected, the family should be questioned carefully. Any inconsistencies in the history of the injury suggest the possibility of child abuse and should be reported to the child protective authorities as required by law. Chronically abused children may have a depressed affect. Furthermore, the pattern of the burn may be suspicious of intentional injury. Scalding burns of the extremities in which the entire foot or hand is burned, with a glove or stocking pattern and lack of splash marks, suggest forced immersion into hot water. Additionally, burns on the back, buttock, or both soles of the feet are highly suspicious for child abuse. The depth of the burn is another factor to keep in mind when abuse is being considered. Partial thickness burns commonly result from accidental scalding. Full thickness burns caused by scalding suggest sustained contact with hot water. Small area, full thickness burns suggest injury from a cigarette. Evidence of other trauma, such as bruising or numerous healed wounds, should be documented.

The first step in management of a burn injury is assessment of life-threatening conditions. The airway must be evaluated immediately for compromise in the case of burns caused by flame or history of smoke exposure. Smoke inhalation can result in severe inflammation of the airways and lungs. Classic signs associated with significant smoke inhalation are burns to the face or nasal hairs and/or carbonaceous sputum. Because the airway can swell rapidly, this condition must be treated aggressively and quickly to prevent airway obstruction. Immediate tracheal intubation is indicated if the patient shows signs of laryngeal edema, such as hoarseness, stridor, or a brassy cough. Endotracheal intubation and mechanical ventilation are required in the case of respiratory failure. Signs of respiratory failure include the development of tachypnea, use of accessory respiratory muscles, and hypoxemia (3).

All patients exposed to smoke in an enclosed space should be screened for carbon monoxide poisoning by measuring a CO level or co-oximetry since an arterial blood gas and pulse oximetry will not adequately identify CO poisoning.

To accurately estimate the depth of skin injury, devitalized tissue must be debrided, and large blisters must be removed. This procedure is usually painful and requires potent analgesics. Burn depth is estimated by careful observation of the wound surface.

The extent of total body surface area (TBSA) covered by second or third degree burns has a great impact on the morbidity and mortality, and must be estimated. Areas of first degree burns are associated with negligible mortality, so the important components of the TBSA are the areas of second and third degree burns. Although time-consuming, the Lund and Browder chart is the most accurate method of determining TBSA. It consists of an anterior and posterior diagram of a patient that is divided into sections which can be colored in according to the distribution of the patient's burns. The TBSA of burn is the sum of the colored areas. Different charts are available for different age groups. An alternative to the Lund and Browder chart is the rule of nines. In this method, the body is divided into eleven

areas of nine percent each. Each upper extremity is 9%, the anterior and posterior portions of each lower extremity are 9%, the anterior upper and lower portions of torso are 9% each, the posterior upper and lower portions of the torso are 9% each, and the neck and head together is 9% to give a total of 99%. The perineum makes up the remaining 1%. However, it must be taken into account that the head is relatively larger and the legs relatively smaller in surface area for children compared with adults. A palm of the hand on one side including the area of the digits, is approximately 1% of the body surface area and can be used to estimate the TBSA of burn.

A burn covering 10% or more of the TBSA of a child is considered a serious burn and should be managed as an inpatient, preferably in a burn unit where specialized expertise is available. Significant burns of face, hands, genitalia, feet, or across the joints are categorized as serious. Transfer to or consultation with a burn center should be considered for these patients.

Management: Any clothing and jewelry should be removed from the area of the burn. If clothing has adhered to the skin, it should be left for removal during the cleansing of the wound (4). Non-adherent material may be cut away. To decrease pain, the burn may be cooled with the application of cooled, sterile, saline-soaked gauze.

Prior to cleaning the burn, analgesia is desirable (4). Burns should be cleansed to remove contaminating debris. Tar or asphalt may be removed with a mixture of cool water and mineral oil (4). Embedded clothing and debris can be removed by irrigation.

Necrotic tissue must be debrided to minimize infection. Removal of necrotic tissue can be accelerated with the use of enzymatic debriding preparations such as collagenase and papain-urea preparations. These preparations may be less painful and may hasten epithelialization. Blisters which have already lysed should be debrided so that the excess skin does not harbor infection. Flimsy intact large blisters are likely to lyse on their own soon, so these can be debrided as well. Small firm blisters can be left alone. The appearance of the burn on the second day almost always looks worse with enlarging blisters. This should be anticipated in counseling.

Patients suffering wounds deeper than a superficial partial-thickness burn should have their tetanus immunization updated. Bacitracin ointment or silver sulfadiazine cream are not necessary in the treatment of superficial burns, but should be used to prevent infection in all other burns.

Once cleansed, the wound should be dressed daily until epithelialization occurs. This will provide some pain relief, protect the wound from infection, and absorb drainage from the wound.

Superficial partial thickness burns heal in approximately 1-3 weeks. Most deep partial-thickness burns eventually heal by epithelialization in 3-9 weeks. Epithelialization begins in the dermis in the remaining hair follicles. As buds of epithelium grow, they eventually merge to close the wound. Hair follicles are destroyed in full-thickness wounds preventing epithelialization. Full thickness burns require surgical treatment consisting of eschar excision and skin grafting.

Severely injured patients are better served at a designated burn center specifically trained in analgesia and wound care for patients with burns. Transfer to a burn center should be considered in more severe burns, major burns to the hands, face, feet, perineum, or complex electrical burns.

If an extremity is involved, immobilization and elevation may be helpful to reduce edema. Edema may increase ischemia and tissue necrosis. Furthermore, compartment syndrome may develop in an extremity that has sustained a circumferential burn. Patients with circumferential burns of an extremity should be admitted to the hospital for observation of the development of this potentially limb and life threatening condition.

Patients with burns covering 10-15% of the TBSA or more, usually require parenteral fluids. Ingestion of fluids may be inadequate in children due to pain, anxiety, and the effects of narcotics. Extravasation of fluid into unburned tissue as well as increased evaporation from the surface of the wound results in hypovolemia. Fluids must be administered to prevent hypovolemia-induced ischemia, lactic acidosis, and shock. Fluid resuscitation with Ringer's lactate or normal saline solution should be administered according to the Parkland formula (7). This formula estimates the fluid requirements of the pediatric patient for the first 24 hours (4 cc/kg for each TBSA percentage point infused over 24 hours in addition to the maintenance calculation), but urinary output is the best indicator of satisfactory hydration. Although adequate fluid administration is essential, it is important to avoid over-hydration. Increased hydrostatic pressure and decreased oncotic pressure from protein loss contributes to the fluid shift, and over-hydration may result in increased wound and whole-body edema (including pulmonary edema and respiratory compromise).

When administering fluid to infants, it is important to appreciate the lack of maturity of their kidneys. Adult glomerular filtration rate levels are not achieved until age 9-12 months. The infant handles fluid overload very inefficiently. Because of an imbalance of maturation of tubular and glomerular functions, the osmolar concentrating ability is estimated to be one half of that seen in adults (6).

Loss of water by evaporation leads to heat loss. Small pediatric burn patients are especially at risk for hypothermia. In order to minimize radiant and evaporative heat loss, the ambient temperature should be kept sufficiently high. IV fluids should be warmed during large fluid infusions. Special care should be taken in patients younger than 6 months old. Children in this age group do not have the ability to shiver. Thermiogenesis is accomplished by catabolism of fat stores requiring large amounts of oxygen. Excessive lactate production and metabolic acidosis may result from prolonged thermiogenesis.

The basal metabolic rate may double after a major burn injury. The increase in metabolic expenditure is roughly proportionate to the surface area burned. For example, a child with a burn covering 50% TBSA requires an increase in the basal level of calories of at least 50%. To decrease the loss of muscle mass, about 20% of the calories administered should be from protein.

Most children sustain electrical burns by the insertion of a metal object into a wall outlet or by exposure to frayed electric cords. Intense heat and deep injuries are produced when the current passes through the tissues. If a child puts a live electric cord into the oral cavity, the lips may be burned. Additionally, the burn may extend completely through the lips and oral mucosa to the labial artery. This can be potentially catastrophic if this artery erodes due to sloughing of necrotic tissue. Sudden hemorrhage can occur as late as one week after injury (1).

Burn injuries may result in scarring and contracture. There is a high risk of scar formation associated with burn wounds that take more than 3 weeks to heal. Furthermore, scars may develop in wounds that heal spontaneously without skin grafting. Children tend to scar worse than adults, and patients with dark skin color, scar worse than patients with light skin. Pressure garments worn 24 hours a day, continuously for one year after healing, may limit the progression of scarring. Joint contractures are characteristic of scarring.

Physical and occupational therapy should begin on the day of admission in order to maximize the cosmetic and functional outcome. If necessary, therapy may continue after discharge for several months as the scar tissue forms and contractures develop. Rehabilitation involves joint positioning, active and passive range of motion exercises, limitation of pressure necrosis, ambulation, and assistance in daily activity. Rehabilitation programs for burn patients consist not only of physical support, but emotional support as well. As the pediatric burn patient matures and enters into new social situations, psychological support may be beneficial.

Questions

1. When is antibacterial ointment indicated?
2. When treating an infant, what are some special considerations that must be acknowledged?
3. When should a patient be sent to a burn unit?
4. How is the %TBSA calculated?
5. What formula is used to determine the amount of fluid administered to the pediatric burn patient within the first 24 hrs?
6. Despite following the above fluid formula, a burn patient has a continuous urine output via urinary catheter of only 0.2 cc/kg/hr (ideally, this should be about 1 cc/kg/hr). The child appears to be moderately edematous. Should the fluid rate be increased or continued at the same rate?

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Answers to questions

1. Antibiotic ointments such as silver sulfadiazine and bacitracin are indicated for all burns except superficial burns.
2. Infants 6 months old or younger are more prone to fluid overload because of their reduced glomerular filtration rates. Additionally, they are more susceptible to hypothermia because they are unable to generate heat by shivering.
3. A patient should be sent to a burn unit if they have serious burns that are beyond the scope of care in the local institution. Examples of this include, second degree burns of 20% TBSA, third-degree burns of 5% TBSA, major burns to the hands, face, feet, perineum, or electrical burns.
4. % TBSA can be estimated by using the rule of nines, the Lund and Browder chart, or by designating the child's palm as 1% of the TBSA. The most accurate method is the Lund and Browder chart.
5. The Parkland formula is used to estimate the amount of fluid appropriate for administration in the first 24 hours.
6. The slow urine output indicates hypovolemia. The fluid infusion rate should be increased to improve the urine output.

Chapter XXI.5. Bites and Stings

Todd T. Kuwaye, MD, MS

A 6 year old female was playing in the yard when she suddenly felt pain in her left ankle. Her ankle became swollen, red and painful, so her mother took her to the pediatrician's office. Upon close examination there is a central puncture lesion with a small amount of serosanguineous drainage. Her vital signs are normal. No other examination findings are present

What are the potential causes for this lesion? What current treatment is needed? What advice should be given to the child and parents?

In Hawaii, we are fortunate to have only a few arthropod bites and stings that are of a medical concern. An arthropod may bite with the use of mandibles or inflict a wound from a stinger. In Hawaii, arthropod bites can occur from mosquitoes, flies, fleas, ants, lice, centipedes, beetles, roaches, and spiders. These arthropod bites are rarely serious except for a few notable arthropods such as the brown violin spider and the black widow spider because of the toxicity contained in their venomous bite. Although bites from these spiders can be serious, they are not as frequent as the bites that occur from mosquitoes, ants, fleas and flies. All bites have the potential to cause local skin irritation, pruritus, swelling, erythema and pain. If not treated well with local skin care, a lesion can also become infected. Local allergic reactions are common from insect bites. Insect bites rarely cause systemic allergic reactions in children when compared to insect stings (1). Although uncommon, if a patient has enough of a repeated allergen load from proteins contained in the saliva of the biting arthropod, systemic allergic reactions could occur (1). Anaphylaxis has been reported from bites of the mosquito, horsefly, and the tick (2).

Another health problem associated with insect bites is the potential to transmit disease. An outbreak of dengue fever in Hawaii (2001) by mosquitoes demonstrated the disease carrying ability of insects as vectors. Another noteworthy vector in Hawaii is the flea and its ability to transmit the plague. Fortunately Hawaii does not have ticks and fleas that carry Lyme disease and Rocky Mountain spotted fever.

Envenomation occurs from such arthropods such as spiders and centipedes in Hawaii. A centipede's bites cause intense localized pain, swelling, and occasionally infection and local tissue necrosis. A few of the spiders in Hawaii contain venom in their bite that can lead to serious complications. Two of the more dangerous spiders are discussed in greater detail below.

The Southern Black Widow Spider (Latrodectus mactans), as well as its cousins, the brown widow (Latrodectus geometricus), and the Western Black Widow (Latrodectus Hesperus), are found in Hawaii (3). The black widow lives in warm, dark, dry places outdoors or in sheds, basements and garages. The Black Widow is a non-aggressive spider, which bites in self-defense. Its venom causes severe muscle cramping which is mediated by a neurotoxin that acts on the presynaptic membrane causing the release and decreased uptake of acetylcholine (4). The victim usually experiences a pinprick sensation, followed by regional lymph node tenderness (30-120 minutes later), a target lesion (at the bite site), and muscle cramping near the bite site (4). Dysautonomia manifested with nausea, emesis, sweating,

hypertension, tachycardia, and malaise can occur (3,8). Symptoms may last 36-72 hours (4). Treatment is analgesia, while supportive care is given to hypertensive and tachycardic patients (4). Antivenom derived from horse serum is available but reserved for the severe cases due to the adverse effects from horse serum administration (4).

The brown violin spider (Loxosceles rufescens) is a cousin of the brown recluse spider (Loxosceles reclusa), which is responsible for most of the clinically significant necrotic spider bites in the United States (5). The Brown recluse spider is not found in Hawaii but the brown Violin spider is found locally (3). All Loxosceles spiders are venomous and produce the clinical condition called loxoscelism, also known as necrotic arachnidism (5). The brown violin spiders are non-aggressive, nocturnal and found under boards and loosened bark (3). The brown violin spider's venom is used to digest its prey, but has both a local and systemic effect in humans, causing dermonecrosis and hemolysis (5). Bites usually are seen in children and can be asymptomatic or it can cause a mild to sharp stinging pain followed by potential development of a central blister to dermonecrosis (5). Systemic reactions include fever, chills, arthralgias, malaise, nausea, emesis, leukocytosis, hemolytic anemia, jaundice, renal failure, shock, DIC and death (5). Systemic reactions are infrequent. Loxosceles envenomation can usually be treated as an outpatient unless there are systemic symptoms, serious infection, or extensive necrosis (5). There is no effective treatment for the dermonecrosis. An antivenom is currently experimental and appears promising (5).

Fortunately, most arthropod bites are more of an annoyance rather than a potential life-threatening situation. Keys to management include prevention of arthropod bites by eradication, avoidance of arthropod's habitats and use of protective clothing. Immediate management may include: local wound care, topical corticosteroids, antibiotics if infected, antihistamines if the lesion is pruritic for comfort and prevention of infection by excoriation, tetanus toxoid booster if not current, and analgesics.

In Hawaii, arthropod stings can occur from bees, wasp, ants and scorpions. All of these arthropods contain mild venoms. However, systemic allergic reactions occur more frequently from insect stings compared to insect bites in children (1). Stinging insects belonging to the order Hymenoptera (bees, wasp, and ants) are responsible for 40-50 deaths a year in the United States (2,7). Reactions to arthropod sting can be classified as usual, large local, anaphylactic and toxic reactions (2). The usual arthropod sting causes the local pain, swelling, and erythema, which resolves in a few hours (2). Large local reactions involve more extensive symptoms, which last 24-48 hours (2). Anaphylaxis is the most serious response (see chapter on anaphylaxis). A toxic reaction occurs from envenomation from multiple stings.

Immediate management is to ensure the removal of the stinger. The stinger of the bee is barbed and detaches after being imbedded into the victim's skin. Since wasps can sting repeatedly, one may find grouped lesions without any visible stinger. The bee stinger contains venom sacs which if pinched can increase the level of envenomation. It is recommended to brush the stinger out of the skin. The usual and local reactions of insect stings require control of pain, pruritus, and swelling, as well as local wound care to prevent infections. Localized hypersensitivity reactions can be treated with topical corticosteroids, urticaria can be treated with antihistamines and anaphylactic reactions are treated more intensively with epinephrine, antihistamines and corticosteroids.

Repeat anaphylactic reactions to insect stings are more common in adults than in children (2). Children under 16 years old, who have isolated allergic reactions (urticaria and angioedema) after stings have a 10% incidence of subsequent systemic reactions and only a less than 0.1% incidence of a life threatening respiratory or cardiovascular allergic reaction (2,7,9). Children's sensitivity to insect venom is expected to diminish over time (2). An allergist should evaluate any child with an anaphylactic reaction to insect stings. Immunotherapy for insects can be used on children depending on the severity of the allergic reaction. However, any child with a history of anaphylaxis and positive skin test or in vitro assay for venom specific IgE should receive immunotherapy for 4-5 years (2). In children with large localized reactions and who are at risk for future frequent or multiple stings, immunotherapy is an option (2). These children should also be given a self-administered epinephrine kit with instructions and a demonstration of its use. Patients should also obtain a medical alert bracelet.

Scorpions are found in Hawai'i, but their stinger contains a venom, which is not significantly toxic. Scorpions from other parts of the world do contain venoms, which can be substantially toxic.

Avoidance of stinging arthropods becomes an important part of management and includes: identification and elimination of stinging insect nests, avoiding brightly colored clothing or strongly scented lotions, wearing shoes or protective footwear outdoors, exercising caution around sites frequented by stinging insects (eaves, attics, and areas where food is present outside), and wearing protective clothing when outside (long shirt, pants, hat, gloves, socks and shoes) (6).

Marine envenomations common in Hawaii occur from box jellyfish, Portuguese man-of-war, and venomous fish. These animals produce protein-based venoms that are used in self-defense or to capture prey. Unfortunately the unwary beach goers may interact adversely with these animals and sustain intensely painful wounds. As a general rule, these venoms tend to be heat labile and can be denatured with heat.

Venomous snakes are not found in Hawaii. A discussion of snakebites is beyond the scope of this chapter.

Questions

1. A ten year old male is stung by a bee. Upon examination of the sting site, a stinger is still embedded in the skin. What should you do?
   a. Pinch it off
   b. Brush it off
   c. Wait till you seek medical attention

2. A twelve year old male moving boxes in the basement experienced a pinprick sensation on his right hand followed by muscle cramps and swelling in his right axilla. On presentation to the ER a target lesion is noted on his right hand. The patient is noted to be nauseated, sweating, hypertensive, and tachycardic. What is the probably culprit?
   a. Centipede
   b. Scorpion
   c. Yellow jacket
   d. Black widow
   e. Brown violin spider

3. True/False: Ticks, flies and mosquitoes can cause anaphylaxis.

4. True/False: Snakes and scorpions are some of the most venomous animals in Hawaii.

5. What two spiders are found in Hawaii that can inflict a serious and potentially deadly envenomation?

6. True/False: Repeat anaphylactic reactions to insect stings are more common in adults than in children.

7. A teenage boy fishing is accidentally poked by a spiny fish. The site becomes red and painful. What are reasonable management steps.
   a. Local wound care
   b. Epinephrine
   c. Application of heat to sting site
   d. Antibiotic ointment
   e. Tetanus toxoid
   f. Contact a poison information center

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Answers to questions

1. b
2. d
3. True, anaphylaxis can occur from any repeated insect bite or sting in which re-exposure to an antigen occurs.
4. false
5. Southern black widow and Brown violin spider.
6. true
7. All except b.

Chapter XXI.6. Common Skin Conditions
Annemarie Uliasz

This is a 6 month old female who is brought to the office with her mother with a chief complaint of a diaper rash for one week. Mother has been using baby powder to keep the area dry, but the rash is worsening.

Upon examination, the buttocks, perianal region, and tops of the thighs appear erythematous with no ulcerations or erosions. Areas of flexure are involved and there are some beefy red areas with a few satellite lesions. The rest of the exam is normal.

Her mother is given instructions to change her infant's diapers frequently, at least every three hours. Baby powder does not keep the area dry once the child urinates, so its value is minimal. Special attention should be made to keep the skin under the diapers dry. Hydrocortisone ointment or cream can be used to suppress the inflammation. Petrolatum or zinc oxide applied to the diaper region is suggested as prophylaxis against irritation. Topical clotrimazole cream is also recommended to eliminate any yeast infection that may be present.

The skin is composed of three different layers. The outer most layer, the epidermis, is made predominantly of keratinocytes. The most superficial layer of the epidermis, the stratum corneum, serves as a protective barrier against the environment, and prevents desiccation. The epidermis also plays a role in immune surveillance (1). Damage to the epidermis increases skin permeability, thereby increasing the risk of infection. The epidermis also contains melanocytes (which gives the skin its color), Merkel cells (which are pressure receptors), and Langerhans cells (which participate in the skin's immune response).

The dermis lies beneath the basement membrane of the epidermis. The dermis consists of collagen, elastin, and proteoglycans, which lend support and durability to the skin. Blood vessels, lymphatics, sweat glands, hair follicles, smooth muscle, and neuroreceptors are all found in the dermis. Fibroblasts in the dermis are responsible for collagen production and are the predominant cell in this layer of the skin. Other cells common in the dermis include mast cells, leukocytes, and histiocytes.

Subcutaneous tissue resides beneath the dermis. This layer serves as insulation, a fat depot, and a cushion against trauma. Blood vessels and lymphatics are found in the subcutaneous tissue as well as the base of hair follicles and sweat glands.

In order to describe a skin lesion, one must have a basic understanding of the language of dermatology. A primary lesion is a lesion that has not been altered by trauma, infection, scratching, therapy, or regression over time. Primary lesions are described as macules, patches, papules, nodules, tumors, vesicles, bullae, pustules, plaques, cysts, and wheals. A macule is a flat, circumscribed skin discoloration that is neither raised nor depressed. It cannot be felt. Once it reaches 1cm or greater in size, it is termed a patch. A papule is an elevated, solid lesion that is less than 0.5cm in diameter. If the diameter is greater than 0.5cm, it is known as a nodule. A nodule is basically a larger, deeper papule. Tumors are usually larger in diameter than nodules, and tend to be variable in consistency and mobility. Vesicles (blisters) are raised, fluid-filled lesions less than 0.5cm in diameter. A bulla is a larger fluid-filled lesion that is greater than 0.5cm in diameter. A pustule is a papule that contains purulent material. A plaque is an aggregation of papules, vesicles, or pustules that is greater than 0.5cm in diameter. Wheals are palpable, firm, edematous lesions that may vary in configuration and size. They tend to be pruritic and evanescent (existing briefly before disappearing). A cyst is a lesion that contains fluid or semi-solid material. Its walls are circumscribed and thick, and it is located deep in the skin.

Primary lesions may develop or turn into secondary lesions. Secondary lesions include crusts, scales, excoriations, fissures, erosions, ulcers, and scars. Crusts (scabs) are dried collections of blood, serum, or pus. They usually arise from a primary lesion such as a vesicle, bulla, or pustule. Scales consist of compressed layers of keratinocytes on the skin surface. An excoriation is a linear erosion caused by scratching. A fissure is a crack in the skin. An erosion is a focal loss of epidermis that heals without scarring. An ulcer is a focal loss of epidermis extending into the dermis that heals with scarring. A scar is an end-stage lesion composed of connective tissue, which may be atrophic or hypertrophic.

Once the definitions of primary and secondary lesions are learned, a skin lesion may be described. The description should include the lesion's size, color, shape, arrangement, distribution, and whether it is a primary or secondary lesion. The following chapter discusses common dermatologic conditions in the pediatric patient.

Contact dermatitis can result from injury to the skin, as in irritant dermatitis, or from a hypersensitivity response, as in allergic dermatitis. The distribution of the rash is determined by the points of contacts. Common hypersensitivity contact dermatitis allergens include latex (rubber), nickel (jewelry, buckles, snaps), hair dye and leather (tanning chemicals). If a particular substance is suspected, a simple test to confirm hypersensitivity is to tape a small piece of it on the medial portion of the upper arm and observe for a reaction 12 hours later.

In the pediatric population, irritant dermatitis is more commonly seen than allergic dermatitis. Irritant dermatitis is an inflammation of the skin caused by exposure to irritants such as soaps, saliva, citrus juice, bubble baths, or detergents (1). The appearance of the skin may range from mild redness, edema, or vesicles to oozing bullae. The face and hands may be affected by saliva from a drooling infant. Bubble baths may be the source of an intense pruritus. Restrictive shoes that trap sweat and moisture may cause irritant dermatitis of the feet. Treatment of contact dermatitis may be as simple as removing the irritant. Hydrocortisone cream will provide additional relief.

Diaper dermatitis (diaper rash) is a common ailment of infants. Diaper rash occurs in approximately 50% of infants. The peak of incidence occurs between the ages of nine and twelve months (2). The main source of irritation is urine and feces on the skin. Diaper dermatitis may occur if diapers are not changed frequently enough, or if the infant has diarrhea. However, it may occur even if diapers are changed regularly. The buttocks, perineal area, lower abdomen and top of the thighs are the areas that are most frequently involved. Characteristically, areas of flexure are spared. The rash appears erythematous, and the skin may look scalded. Ulcers and erosions may be seen in severe cases. Diaper rash may be treated by frequent changes of diapers, at least every three hours, and close attention to keeping the skin dry. Most cases are self-limited and resolve in 3 days (3). Petrolatum or zinc oxide may be used as a protective barrier. Severe cases may be treated with low potency topical corticosteroids. Diaper rashes may be complicated with a secondary Candida infection. Candida albicans can complicate any diaper rash that has been present for three or more days (4). In these cases, the rash involves the skin flexures with satellite lesions. These rashes may be treated with anti-candidal agents (e.g., clotrimazole, miconazole and nystatin).

Erythema toxicum, a skin eruption which occurs in roughly half of all newborns, usually within the first two days of life (5). It is self-limited, lasting approximately three days. The etiology is unknown. Erythema toxicum presents as papules, macules, and sometimes pustules surrounded by an irregular halo of erythema. The lesions are distributed on the arms, legs and trunk. A Wright stain of a smear (by pricking the skin and doing a touch prep on a slide) reveals eosinophils with no organisms present (3).

Nevi (moles) are clusters of melanocytes that appear at the epidermal-dermal junction. The number of acquired nevi increases with age, reaching a plateau in the 30s or 40s (1). An adult will have on average 25-30 nevi. The amount of nevi that develop is related to the amount of sun exposure sustained in childhood. Although most nevi are benign, a small percentage may undergo malignant transformation into melanoma. Risk of melanoma increases as the number of nevi increases and as the amount of sun exposure increases. Malignant change may be suspected if the nevi display irregular borders, large size (5-15mm), multiple colors, or become ulcerated, scaled, or indurated. If any of these suspicious characteristics are observed, the nevus can easily be excised. A complete skin examination is recommended for children with atypical nevi. These children should be counseled regarding limiting sun exposure.

Paronychia is inflammation of the nail folds of the fingers. Acute paronychia may occur spontaneously, or after trauma, removal of a hangnail, or nail-biting (6). Staphylococci or streptococci infections are often responsible for acute paronychia. The patient presents with warmth, edema, erythema and proximal nail fold tenderness. Treatment includes warm soaks (to soften the skin), oral antibiotics, and drainage of an abscess if one is present. The chronic form is more commonly seen in children and is often caused by finger sucking, which creates a desirable environment for yeast, such as Candida, and bacteria to thrive (7). In chronic paronychia, the nail fold (eponychium) will swell and then separate from the underlying nail plate. Foreign material present under the nail leads to inflammation and infection. Treatment includes reducing predisposing factors, careful attention to hand drying, incision and drainage of the pus, and topical anti-inflammatory agents. Antibiotics may be employed empirically or until the cultures come back (most likely Staph aureus) (7).

Varicella zoster (chickenpox) is spread via respiratory secretions and direct contact with cutaneous lesions. Routine varicella immunization has drastically reduced the incidence of this infection. The incubation period is approximately 2 weeks (10 to 21 days). Subsequently, a pruritic, vesicular rash originates on the scalp or trunk and spreads to the rest of the body. Macular or papular lesions appear which develop into vesicles. The lesions of varicella zoster are sometimes described as "dew drops on a rose petal" (8). The vesicles then dry up and become crusts, which persist for three weeks before disappearing. Typically, there are lesions in various stages of healing. Children are contagious from two days before to five days after the onset of the rash. A Tzanck smear may be helpful in confirming the diagnosis (reveals multinucleated giant cells) (6), but this is usually unnecessary. Complications include secondary infection with staphylococci or streptococci. Varicella encephalitis may occur shortly after the appearance of the rash, most commonly presenting with mild ataxia. However, the prognosis is usually good, unlike the encephalitis caused by herpes simplex virus. Immunocompromised patients with varicella zoster infections may experience persistent vesicular eruptions that may become hemorrhagic or they may experience disseminated varicella. It is recommended that high-risk individuals (immunocompromised) receive human varicella zoster immunoglobulin (VZIG) following exposure to chickenpox. Additionally, neonates whose mothers develop chickenpox within five days prior to or two days following delivery should receive VZIG as well as premature neonates born less than 30 weeks gestation who have been exposed to chickenpox. Acyclovir may be administered in cases of severe varicella, but some advocate routine use of acyclovir for varicella or zoster, especially for adolescents due to their propensity to develop severe disease. Because of the risk of Reye syndrome, aspirin should be avoided.

Once chickenpox subsides, the virus becomes latent. Latent varicella may reactivate causing herpes zoster. Herpes zoster, or shingles, is characterized by groups of vesicles distributed along a cutaneous nerve (a dermatome). The thorax is most commonly involved, but lesions may appear along any dermatome. Involvement of the face, neck, and eye can be serious. New crops of vesicles may appear for three to five days. As in chickenpox, the vesicles dry up into crusts and disappear within three weeks.

Five to ten percent of children develop cutaneous warts (1). Common warts, typically found on the hands, are caused by HPV (human papilloma virus) types 1, 2, 4, and 7 (9). Common warts are flesh-colored, rough, and hyperkeratotic. When the superficial surface is excised, many black dots may be visible. These black dots are actually loops of capillaries. Plantar warts are found on the soles of the foot. They are often compressed against the surface of the foot due to continual weight bearing pressure and may be painful. Plantar warts are caused by HPV types 1and 2. Flat warts, or verrucae planae, are caused by HPV types 3 and 11. They are slightly raised, typically less than 3mm in diameter, and appear in crops of 10-30 or more. Their color ranges from pink to brown, and may occur on the forehead and dorsum of the hand. Condyloma acuminata are warts that are found in the anogenital region. They are most commonly seen in the sexually active adolescents. In a young child, these warts may have been transmitted through the birth canal, through spread from cutaneous warts, or they may signify child abuse. Condyloma acuminata are caused by HPV types 6, 11, 16, 18, and 31. Types 16, 18, and 31 are associated with cervical cancer. Condyloma acuminata are moist, soft, papillomatous lesions that may occur as single or multiple lesions. If untreated, they may grow to cauliflower-like masses. Genital warts are covered in the chapter on sexually transmitted infections.

Over fifty percent of warts regress spontaneously within two years. However, untreated warts have the potential to spread and progress. When treating warts, it is imperative to protect the surrounding skin from irritation. Prior to treatment, plantar, palmar, and common warts should be pared down until the capillaries are revealed. This makes the warts more responsive to treatment. It is recommended that therapy be administered every two weeks. Liquid nitrogen or cantharidin may be used to treat common warts as well as light electrodesiccation and curettage. Common warts and plantar warts may respond to lactic acid or salicylic acid treatments (over the counter topical wart medication). These warts may also be soaked in warm water and reduced with a pumice stone. Successful treatment with duct tape has also been reported. Condyloma may be treated with podophyllin applications every two weeks. However, if the warts are refractory, liquid nitrogen or CO2 laser treatment may be necessary.

Molluscum contagiosum is a viral infection of the skin caused by a DNA containing pox virus. It is most commonly seen in children. Boys are more commonly affected than girls are. The peak incidence is at age ten years (2). The lesions are small, firm, skin-colored papules that are centrally umbilicated. They may appear as one or multiple lesions, and tend to be approximately 1-5 mm in diameter. The papules may occur anywhere on the body, but are usually found on the trunk, face, arms, and genital region. Molluscum contagiosum may be spread by direct contact, or by autoinoculation. This infection typically spontaneously resolves within six to nine months, however, treatment may prevent autoinoculation and person to person spread (1). Treatment includes curettement, electrosurgery, cryosurgery, or other standard wart medications. Instructions on washing it well (to prevent spread) may be all that is necessary.

Pediculosis, commonly known as lice, affects people of all ages. There are three types of lice: body or clothing lice (Pediculus humanus corporis), head lice (Pediculus humanus capitis), and pubic or crab lice (Phthirus pubis). Pruritus is the hallmark of all types of pediculosis. Lice bite the skin and live on the blood. They cannot survive without human contact. The female louse lays eggs, which may be seen attached to hair follicles or clothing fibers. Once the eggs hatch, the newly born lice mature in 30 days (1). The female louse lives another thirty days and deposits a few eggs each day. The diagnosis is made by identifying lice or eggs (nits) on the hair shaft or clothing fibers. The nits are small white oval-shaped capsules.

Body lice is rare in children. It may be seen in conditions of poor hygiene, especially in colder environments when the opportunity to change clothes regularly is lacking. The lice are transmitted on contaminated clothing or bedding. They are found on the skin only

transiently when they are feeding. At other times, the nits are firmly attached to the seams of clothing. The primary lesion found on the shoulders, trunk or buttocks, is a small, red macule or papule with a central hemorrhagic punctum. Treatment consists of improved hygiene and washing all infested clothing and bedding in hot water. Alternatively, the lice will starve if clothing is stored at 75-85 degrees F for two weeks. For those unable to change clothes, clothes may be dusted with 10% lindane powder. Lindane lotion or permethrin cream may be applied for 8-12 hours to eradicate eggs and lice on body hair.

Head lice infest the scalp hair. It is especially bothersome among school children. Patients often present with scalp itching. If the eyelashes are involved, conjunctivitis may result. Transmission occurs by head-to-head contact, and shared combs, brushes, or towels. Translucent eggs are laid near the proximal portion of the hair shaft. Treatment involves application of 0.5% malathion (Ovide) to the hair for 12 hours (although application for much shorter periods may be sufficient). The hair is then washed, and the dead nits are then removed from the hair shafts by a fine toothed comb. Clothes must be laundered or dry-cleaned. Other shampoo treatments include permethrin 1% creme rinse (Nix or Elimite), pyrethrin shampoo, or 1% lindane shampoo (Kwell). Lindane is potentially neurotoxic so it is not recommended for infants and young children. These shampoos are applied and rinsed after 10 minutes, with a repeat application 7-10 days later. There are presently no published trials assessing the safety or efficacy of alternative treatments such as herbal remedies, kerosene, or battery-powered combs. Occlusive dressings are sometimes recommended using mayonnaise or petroleum jelly, but their efficacy is not thoroughly studied.

Pubic lice (crabs) is transmitted by skin-to-skin or sexual contact with an infested individual. The infestation is usually encountered in adolescents, although small children may occasionally acquire pubic lice on the eyelashes. Pubic lice are only 1-2 mm in length (body and head lice are 2-4 mm in length), and are greater in width than length, giving them a crab-like appearance. Treatment includes a 10 minute application of a pyrethrin preparation. Retreatment may be necessary in 7-10 days. Lindane shampoo, which requires a 10 minute application time, is an alternative choice. Eyelash involvement may be treated by petrolatum applied three to five times per day for 8-10 days. Clothing, bedding, and towels should be thoroughly washed or dry-cleaned.

Scabies is caused by the female Sarcoptes scabiei mite. A papular and vesicular rash is seen as a result of the mite burrowing into the stratum corneum. The mites burrow approximately 2mm (1). Itching occurs two to six weeks after infestation, and may be more intense at night when the mites are more active. Lesions are most commonly seen between the fingers and toes, axillae, flexor surfaces of the wrists, belt line, and areas surrounding the nipples, genitals, and buttocks. A diagnosis of scabies is made based on a history of itching and the characteristic lesions. A definitive diagnosis is made upon identification of the adult mite, ova, or larvae upon microscopic examination of skin scrapings from the lesions, but this is rarely done in general pediatric practice. The patient should bathe thoroughly and the involved areas should be scrubbed with a brush. Permethrin cream (Elimite), lindane lotion (Kwell), or crotamiton (Eurax) lotion may be applied, and the patient should be dressed in clean clothing. Bedding should be cleaned and other family members should be questioned and inspected to determine if they are infested as well. Scabies may persist for months in patients who are untreated.

Mosquito bites and flea bites are common sources of skin irritation in children. Fleas tend to bite multiple times in one area, whereas mosquitoes usually bite in random widely dispersed areas that are not covered by clothes. The irritation that stems from an insect bite is due to a localized hypersensitivity reaction. Treatment of mosquito and flea bites consists of cool compresses, calamine lotion, topical hydrocortisone and oral antihistamines to provide relief from the pruritus. Insect repellants may be used on exposed skin as prophylaxis. DEET containing mosquito repellants are effective, but DEET is potentially neurotoxic so it should be applied judiciously. Using clothes to completely cover the skin may be safer. Fleas may be eradicated by treating pets and decontaminating the house.

Questions

1. Name the three layers of skin. Name three functions of skin.
2. What organism is responsible for the development of warts?
3. What are the two organisms responsible for infection in acute paronychia?
4. What is the treatment for lice?
5. Who should receive varicella zoster immunoglobulin?
6. What characteristics of a mole are suspicious for malignant melanoma?

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Answers to questions

1. The three layers of skin are the epidermis, dermis, and subcutaneous tissue. The skin serves as a barrier against the environment, protection against desiccation, and plays a role in immune surveillance.
2. Human papilloma virus is organism responsible for the development of warts.
3. Staph aureus is responsible for most infections in acute paronychia.

4. Pediculosis is treated with a shampoo such as 0.5% malathion rinse, permethrin 1% creme rinse, 1% lindane shampoo, or pyrethrin. After the shampoo is rinsed, the hair is combed with a fine toothed comb to remove dead nits. Clothes and bedding must be washed in hot water.

5. Varicella immunoglobulin should be given to immunocompromised individuals, neonates whose mothers develop chickenpox within five days prior to or two days following delivery, and premature neonates born less than 30 weeks gestation who have been exposed to chickenpox.

6. Suspicion of malignant transformation of nevi should arise upon observation of irregular borders, variegated color (multiple colors), size greater than 5-15 mm, and any change in texture including crusting, ulceration, or induration.

Chapter XXII.1. Statistics
Loren G. Yamamoto, MD, MPH, MBA

The mother of a 15 month old boy is brought to the clinic because of fever. His temperature has been up to 40 degrees (104 degrees F). He has a slight cough, but no vomiting or diarrhea. His urine output is normal without urinary complaints. Mother has given him acetaminophen which results in some improvement. His past medical history is unremarkable. He is generally healthy.

Exam: VS T 39.8 (103.6), P120, R 35, BP 90/60, oxygen saturation 99% in room air. Height and weight are at the 50th percentile. His examination is normal except for mild nasal congestion. His tympanic membranes are normal.

You believe that he most likely has a viral infection, but you are told that occult bacteremia is a possibility. Since this is a clinically occult phenomenon, you decide to do a study to determine if a CBC is useful in predicting whether occult bacteremia is present. You put together an institutional review board (IRB) study proposal which is approved. 400 febrile patients are enrolled in the study. They all have CBCs and blood cultures drawn. Out of the 400 patients, 20 have positive blood cultures. The mean white blood count (WBC) in these 20 bacteremic patients is 16.8 (standard deviation=7.3). The mean WBC in the other 380 patients is 13.9 (standard deviation=6.2). p=0.04 which means that the probability that this difference is due to chance is only 4% (0.04). Thus, there is a 96% chance that this difference is real, which means that the WBC in bacteremic patients is significantly higher than in non-bacteremic patients. Believing that your study results are astounding, you decide to present this information to the hospital chief of staff summarized as follows:

	ALL	<10.0	10.0-14.9	15.0-20.0	>20.0
Positive BC patients:	20	4	5	6	5
Negative BC patients:	380	120	110	90	60

All of a sudden, the results do not appear to be as astounding as initially thought. If a child has a WBC >20.0, most of the patients still have negative blood cultures. Additionally, 9 out of the 20 bacteremic patients had WBC counts less than 15.0.

There are two basic types of data: 1) continuous variables which can take on any value within a reasonable range (e.g., age, weight, blood pressure, peak flow, oxygen saturation, cholesterol, etc.), and 2) discrete (or categorical) variables (e.g., sex, ethnicity, socioeconomic status, medical insurance, etc.) which can only take on values of discrete categories. Data types are important because this determines which type of statistical test(s) to run.

Notice that most continuous variables can be converted into discrete variables by grouping them in ranges. For example, age groups can be formed: 1) 0-1 yr, 2) 2-5 yrs, 3) 6-10 yrs, 4) 11 yrs and above. Cholesterol values can be categorized into high cholesterol versus low cholesterol. Discrete variables cannot usually be converted into continuous variables. However, some discrete variables have rank order while others do not. For example, medical insurance has a particular rank order: 1) no insurance, 2) medicaid insurance, 3) private insurance. Military rank order is another discrete variable that has rank. Socioeconomic status could have rank as well: 1) unemployed, 2) blue collar, 3) white collar. Discrete variables such as race, hair color, political party, etc., have no inherent rank order.

Statistics are basically either descriptive or inferential. Descriptive statistics are summary numbers use to describe a set of data. If 1000 data measurements are obtained, it would be impractical to list all 1000 measurements in your publication. It would be more efficient to present a few summary numbers which describe the 1000 data measurements. These are descriptive statistics. Descriptive statistics for continuous variables include: mean, standard deviation, range, mode, median, etc. The mean, mode and median describe the central tendency of the group of observations. The range, standard deviation and confidence interval describe the spread of the observation measurements. For example, for a set of 1000 cholesterol measurements, the mean is 100, the range is 40 to 310, and the standard deviation is 45. Descriptive statistics for discrete variables include rates and frequencies (numerator/denominator). For example, 30% of the group has black hair.

These descriptive statistics can be graphically compared to determine if two sets of observations are different. The means represent the center of two bell shaped curves. A small standard deviation means that the shape of the bell is very narrow. A large standard deviation means that the shape of the bell is very wide. One standard deviation from the mean estimates the point of inflection (where the curve changes from convex down to convex up) of the bell shaped curve. The mean plus or minus two standard deviations should contain approximately 95% of the observations (or area under the curve). If the two bells have substantial overlap, then the two groups are most likely, NOT significantly different. If the two bell shaped curves have almost no overlap, then the two groups are most likely, significantly different.

The 95% confidence interval can be calculated to determine the likely range of the true mean. The mean of a sample estimates the true mean. The 95% confidence interval calculates the range of possible values for the mean with 95% confidence (i.e., there is a 95% chance that the true mean lies within the 95% confidence interval). A wide range or interval means that there is great uncertainty about what the true mean is (large variance), while a narrow 95% confidence interval means that there is great certainty about what the true mean is. The 95% confidence interval is similar to graphing two distributions because if the 95% confidence intervals of two groups exclude each other, then the two groups are significantly difference. For example, group A has a mean of 25 and group B has a mean of 30. The 95%CI for A is 23 to 27, while the 95%CI for B is 28 to 32. The two groups are significantly different because the two 95%CIs exclude each other. But if the 95%CIs were 20 to 30 and 27 to 33, then they overlap, so the two groups are probably not significantly different.

Inferential statistics compare two or more groups of observations to determine if the groups are significantly different (or related) or NOT different, in a more mathematically precise way. Nowadays, these tests are all done by computer software. It is not really useful to know the formulas for calculating the test results. The concepts of which test to use and how to interpret the results are more important. The selection of a statistical test seems perplexing, but in its basic form, it is rather simple. Since there are only two types of data (continuous and categorical), comparing variables can only take on a limited number of combinations. A basic guide is as follows:

Comparing a continuous variable between two groups: T-test.

Comparing a continuous variable between more than two groups: Analysis of variance.

Comparing a discrete variable between more two groups or more: Chi-square.

Determining the relationship between one continuous variable and one or more continuous variables: Regression (linear regression for two variables, multiple regression for more than two variables).

Although we often use inferential statistics to determine if two groups of observations are different, statisticians utilize a non-intuitive concept called the null hypothesis, which hypothesizes that the two groups are the same. If we are trying to determine if something is different (which is the usual case), you can think of the null hypothesis as the opposite of what we are trying to show. For the example of the study of WBCs and bacteremia, the null hypothesis is that the WBCs in bacteremic and non-bacteremic febrile children are the same.

The commonly cited p value is the probability that the difference demonstrated is due to chance alone. Statisticians have selected p=0.05 (or 5%) as an arbitrary cut off value. If p<0.05, then the difference is said to be statistically significant because the probability that this difference is due to chance alone is less than 5%. If this probability is greater than 5%, then this probability is too high for the difference to be statistically significant.

If p<0.05, the statistical terminology is that we reject the null hypothesis. Recall that the null hypothesis was that the WBC counts in bacteremic and non-bacteremic febrile children are the same. So by rejecting the null hypothesis, we are concluding that the WBCs in bacteremic and non-bacteremic children are different (i.e., significantly different such that we can reject the null hypothesis).

The null hypothesis is non-intuitive (seemingly backward thinking) to most non-statisticians. It might be easier to think of the p value as the significance level. If p is <0.05 (or 5%), then this difference is said to be significant. If p is >0.05, then this probability is not small enough, so the result is said to be non-significant.

These statistical tests are best understood by example. A study is undertake to determine which alien species is smarter: Jupitrons or Zoobies. IQ tests are performed on 1000 Jupitrons and 800 Zoobies. The mean IQ for the Jupitrons is 110 (standard deviation 30), and the mean IQ for the Zoobies is 120 (standard deviation is 75). A T-test is done which determines the p value to be non-significant. Although the Zoobies have a higher IQ, their standard deviation is large which means that there are a lot of smart Zoobies and a lot of not-so-smart Zoobies. The standard deviation for the Jupitrons is smaller, so the spread of Jupitron IQs is narrower. Since p is larger than 0.05, we must accept the null hypothesis and conclude that the IQs of Jupitrons and Zoobies are not different (i.e., they are the same). If p were 0.02 instead, then we would reject the hypothesis and conclude that the IQ levels of Jupitrons and Zoobies are significantly different.

Another alien group, the Dimbos, are added to the comparison. 1000 Dimbos are studied and their mean IQ is 68 (standard deviation 22). The three groups, Jupitrons, Zoobies and Dimbos are compared using analysis of variance (ANOVA): p=0.01, which means that at least one of these groups is different from the others. In this case, it is quite obvious that the Dimbos are less intelligent than the Jupitrons and Zoobies, but in some other instances, it may not be that obvious. If 10 different groups are tested and p is significant, this could mean that the lowest group is different from the highest group, but other groups may be different from the others as well.

Compare the T-test to ANOVA. The only difference is that the T-test tests two different groups and ANOVA tests three or more groups. What if we did an ANOVA test, but only used two groups? It turns out that this is mathematically identical to the T-test. So whether you select a T-test or ANOVA for the comparison of two groups, the statistical calculation and the p value will be the same.

Jupitrons have hearts too, so a study is done to compare heart attack (acute myocardial infarction) rates in Jupitrons and Humans. Out of the 1500 Jupitrons residing on the planet colony Vlazer, 15 have sustained myocardial infarcts (MI) (1%). This compares to the 3000 Humans residing on Vlazer of whom, 90 have sustained MIs (3%). A chi-square test is done to determine if the 3% MI rate in Humans is significantly higher than the 1% MI rate in Jupitrons. These results form a 2 by 2 table which looks like this:

Species	MI	No MI	Total	MI rate
Humans	90	2910	3000	90/3000 = 3%
Jupitrons	15	1485	1500	15/1500 = 1%
Total	105	4395	4500	

The clinical question is: Do MIs occur more frequently in Humans? The 2 by 2 table above can be related to an "expected values" table. If the species (Human versus Jupitron) is unrelated to MI (in other words, there is no relationship between MI and species, or the MI rates are the same in both species), the numbers in each of the cells of the 2 by 2 table should distribute randomly. The expected value in each cell should be the row total multiplied by the column total, divided by the grand total. The expected values table should look like this:

Species	MI	No MI	Total
Humans	70	2930	3000
Jupitrons	35	1465	1500
Total	105	4395	4500

The expected value for the Human MI cell is calculated by multiplying the row total (3000) by the column total (105), all divided by the grand total (4500).

3000 X 105 / 4500 = 70

The actual value in this cell is 90. So this deviates from the expected value by 20. The differences between the true values and the expected values in each cell are squared and added together. This forms the numerator for the chi-square value. The larger the chi-square value, the smaller the p value. The 2 by 2 table is a reasonably simple calculation by hand, but nowadays, all of these calculations are done by computer. The p value for this particular set of data is <1% (p<0.01), which is significant, so we conclude that the MI rates in Humans is significantly different from that of Jupitrons (i.e., we reject the null hypothesis that the MI rates in Humans and Jupitrons are the same).

A similar methodology can be used if there are more than two groups and more than two possible outcomes. For example, comparing MI rates in Humans, Jupitrons and Zoobies would result in a 2 by 3 table. Comparing hair color in Humans, Jupitrons and Zoobies would result in a 4 by 3 table assuming that there are 4 possible hair color types.

Note that so far, we have compared a continuous variable by a categorical variable (IQ by alien species using a T-test or ANOVA), then a categorical variable by a categorical variable (MI by alien species using the Chi-square method). The only other possible combination is to compare a continuous variable by a continuous variable. The method used here is regression. In the selection of a statistical test, there are only three possibilities: 1) continuous by categorical, 2) categorical by categorical, and 3) continuous by continuous. The selection of a statistical test is not that hard after all.

Regression analysis determines the degree of correlation that one continuous variable has with another. An example would be age and weight. Of course these have some degree of correlation, so such a study would show statistically significant correlation. Regression analysis generates a correlation coefficient (called r). The correlation coefficient (r) can range from -1 to 1. If r is positive, this means that as one variable goes up, the other variable goes up. Age and weight would be an example of this. If r is negative, this means that as one variable goes up, the other variable goes down. Birth weight and hospital length of stay is an example of this because low birth weight tends to result in longer hospitals lengths of stay. An r value of 1 or -1 implies perfect positive or perfect negative correlation, respectively. An r value of 0 indicates that there is no correlation between the two variables tested. Regression analysis also calculates a p value. The p value is the probability that the r value is 0.

For example, if the r value is 0.1 and p=0.01, then there is significant correlation, because p is <0.05, which means that the r value is significantly different from zero. If the r value is 0.5 and p=0.4, then there is no significant correlation even though the r value is larger, because p is too high, which means that there is a 40% probability that r could be zero. A large r value with a large p value is often seen with regression analysis with only a few observations (an inadequate sample size).

If the regression analysis involves only two variables, this is called linear regression. If the regression analysis involves more than two variables, then this is called multiple regression, in which case, one variable must be considered a dependent variable and the other variables must be independent variables, such that:

$$D = Q + aX + bY + cZ$$

In the above equation, D is the dependent variable, Q is a constant, XYZ are independent variables, and abc are factors which determine the effect of XYZ on D. An example of this is a study which attempts to determine the environmental factors that result in wheezing. D=the number of children wheezing on a given day. X=the amount of viral infections in the community on that day, Y=the bad weather index as measured by that day's barometric pressure, and Z=the amount of air pollution (dust, pollutants and volcanic dust present) that day. All three of these factors affect the amount of wheezing in the community. Terms a, b, and c can be thought of slope terms for the model, but they are not the correlation coefficients. Separate correlation coefficients and p values would be determined for each independent variable X, Y and Z to determine the degree of correlation (the r value) and whether the correlation is significant (p value) for each of X, Y and Z.

All the statistical tests that have been described so far, have a few assumptions. A basic assumption is that the data is distributed in a "normal distribution" (resembling a bell shaped curve). This assumption is usually not true. However, the central limit theorem (no need to describe this here) usually allows us to use these tests if the distribution is "somewhat normal" and there are enough observations (data points). If a normal distribution is clearly not present, then, we must use "non-parametric" tests (e.g., Wilcoxon rank-sum test, Mann-Whitney U test, etc.). So the selection of a statistical test is not quite as simple as what was described earlier.

There are two types of statistical errors knows as type 1 and type 2. The type 1 error is the probably of incorrectly concluding that a true difference exists. The probability of a type 1 error is known, measured by the p value. In the case example, the probability of incorrectly concluding that, the WBC counts in bacteremic versus non-bacteremic patients is different, is 4% (p=0.04).

The type 2 error is the probability of incorrectly concluding that the two groups are the same (i.e., no difference exists). Unfortunately, there is no foolproof way to measure this type of error accurately. If one concludes that no difference exists because p>0.05, then there are two possible realities. One reality is that the two groups are the same and the conclusion that no difference exists, is correct. The other possible reality is that the two groups are different, but because of an inadequate sample size, the study was unable to show that p<0.05. For example, if we undertook a study to determine if males were taller than females, and we took a random sample of 6 adults (3 male and 3 female), the mean male height is 173 cm and the mean female height is 163 cm. In this case p=0.15. We conclude that there is no significant difference in male and female heights. A type 2 error has occurred here. We know that there should be a difference. Yet the p value has not achieved statistical significance (p is not less than 0.05). This is due to an inadequate sample size. With only three data points in each group, it is intuitively obvious that more subjects in each group would be necessary.

Whenever an inferential statistical test concludes that no significant difference exists, it is customary to perform a "power calculation" which approximates the probability that the conclusion of "no significant difference" is correct. A large sample size has greater statistical power adding to the strength of the conclusion that no significant difference exists. How many subjects or observations does one need to avoid type 2 errors? This gets into the discussion of sample size determination. This is a rather complex subject, but suffice it to say that it requires several assumptions.

a) How do we know if a true difference exists? If one truly does NOT exist, it would take an infinite number of data observations to achieve statistical significance. Since we don't really know if a true difference exists (that's why we're doing a study), how can we really determine the sample size?

b) What is the true variance (std. deviation, etc.) or scatter of the real life data? If the scatter is wide, we need a large sample size. If the scatter is narrow, then we can get by with a smaller sample size. But we often do not know what the actual variance is. Then how can we determine a sample size before the study?

So to estimate a sample size before a study is done, we must guess that if a difference exists, it must be approximately as large as our assumption guess. Also, we must guess at what the spread (variance) of the data must be. If we make these two assumptions, we can estimate the sample size.

Just because something is statistically significant, does not necessarily mean that this is clinically important. In the WBC/bacteremia example in the case, bacteremic patients were shown to have significantly higher WBC counts compared to non-bacteremic patients. Look at the actual numbers again:

	ALL	<10.0	10.0-14.9	15.0-20.0	>20.0
Positive BC patients:	20	4	5	6	5
Negative BC patients:	380	120	110	90	60

As we know, in any single case, the WBC is not very predictive because there is too much overlap. Note that MOST of the patients with WBC>20.0 have negative BCs. Also, nearly half of the bacteremic patients had WBCs lower than 15,000. Statistical significance does not always indicate clinical importance.

Most studies perform multiple statistical tests. Using $p<0.05$ as a cutoff value for statistical significance, means that each "statistically significant" result has a 5% chance of being due to chance alone (i.e., wrongly concluding that a difference actually exists). The more tests that are run, the more like it is that one will, by chance, wrongly find a "statistically significant" result. When multiple tests are performed, this phenomenon should be acknowledged. Prior to running the statistical tests, it may be more optimal to set statistical cutoff values at something less than 5% (e.g., 1%). The means to correct for the phenomenon of multiple tests has been supported by some editorials in the literature. Just realize that the problem exists and perhaps acknowledge it, form a crude means to correct it, or get a statistical expert to find an acceptable way of correcting it.

Optional paragraph (feel free to skip this entire paragraph, because the concept discussed in this paragraph is somewhat difficult to grasp): Note that the conclusion in the case example, is that the WBCs in the two groups are different. "Different" means greater than or less than. Although we know that the mean WBC in bacteremic patients is higher than the mean WBC in non-bacteremic patients, the probability of 4% ($p=0.04$ in the case example) means that the probability that the difference is due to chance is 4%. If we knew ahead of time, that if a difference exists, then we would expect the WBC in bacteremic patients to be higher and not lower, then we are actually only interested in checking one side of the "they are different" relationship (i.e., that the WBC count is higher in bacteremic patients). We are NOT interested in investigating the possibility that the WBC count is lower in bacteremic patients. This is a rather subtle difference and this concept is difficult to understand. This refers to the concept of the single sided test versus the two-sided test (also know as two tailed). Computer generated p values are always two-sided probabilities since the assumption is that we are performing a two tailed test. The two tailed probability is for the conclusion that the WBC is different in bacteremic patients. The single sided probability is that the WBC is greater in bacteremic patients. So the probability that the different WBC in bacteremic patients is due to chance is 4% ($p=0.04$). The probability that higher WBC in bacteremic patients is due to chance is 2% (half of the two tailed probability). This concept can be very important if your p value is for example 8% ($p=0.08$) which is not considered statistically significant. However, if you appropriately use a single sided probability, then $p=0.04$ which is statistically significant. The major issue here is that the null hypothesis must be stated properly prior to determining the probabilities. This is somewhat complex and beyond the scope of this chapter.

Questions

1. You have interviewed 50 children who have been hospitalized for bicycle related head injuries and found that 14 of them were wearing a bicycle helmet at the time of the accident. In a control group (children without injuries riding their bicycle on a community bicycle path), you observe the first 100 children and note that 92 of them are wearing bicycle helmets. What descriptive statistics should be described here? What inferential statistical test should be done?

2. If the result of the inferential statistical test for the example above is $p=0.001$, what conclusion can be drawn?

3. What would the null hypothesis be for the example above?

4. Indicate whether the following are categorical variables or continuous variables?
    a. Type of health insurance.
    b. Cholesterol.
    c. Oxygen saturation.
    d. Respiratory rate.
    e. Subdural hematoma.
    f. Lumbar puncture result.
    g. Cervical spine fracture.

5. You are doing a study on oxygen saturation values in asthmatics presenting to an emergency room. You find that asthmatics who are eventually discharged home had a mean oxygen saturation of 95.6% at initial presentation, but the asthmatics who require hospitalizations presented with a mean oxygen saturation of 94.5%. What are the descriptive statistics that should be presented? What inferential statistical test should be used here?

6. In the example above the p value is found to be 0.001. This is considered highly significant since the p value is so small. Comment on whether this highly significant result is clinically important?

7. Is the oxygen saturation measurement distributed in a normal fashion? In other words, if you plotted a value of oxygen saturation for 10,000 patients, would the shape of the distribution be bell shaped? Explain why or why not.

8. Without doing a statistical test, indicate whether you think the following examples show groups that are significantly different or not and justify your answer:
    a. Mean IQ in two groups are 90 and 120. The standard deviation is 45 for both groups.
    b. Mean weight in two groups are 45 and 55 kilograms. The standard deviation is 3 for the first group and 2 for the second group.
    c. Mean oxygen saturations in two groups are 94% and 97%. The standard deviation is 2% for both groups.

References

1. Glaser AN. High-Yield Biostatistics, 2nd edition. 2001, Philadelphia: Lippincott Williams & Wilkins.
2. Hildebrand DK, Ott L. Statistical Thinking for Managers, 2nd edition. 1987, Boston: Duxbury Press.

Answers to questions

1. Descriptive statistics are the rates of bicycle helmet use in the injured group and in the control group. The proper inferential statistical test to use is a chi-square test.

2. The rate of bicycle helmet use in the injured group is significantly different from that in the control group. It might be tempting to say that bicycle helmets prevent significant head injuries from this study, but such a study is not good enough to conclude this.

3. Bicycle helmet use rates in the two groups are the same.

4a. Categorical.

4b. Continuous.

4c. Continuous.

4d. Continuous.

4e. Categorical. The patient either has it or they don't.

4f. This could be both depending on what we mean by this. This would be a continuous variable if we are referring to the CSF WBC count, the RBC count, the CSF glucose, or the CSF protein. This would be a categorical variable if we are considering the CSF to be normal or abnormal, or if we are considering the gram stain result (organisms versus no organisms).

4g. Categorical. The patient either has it or they don't.

5. The basic descriptive statistic is the mean oxygen saturations in each group. Other commonly cited descriptive statistics are the standard deviations and the ranges for each group, which would describe the spread of the data. The inferential statistical test would be a T-test or ANOVA.

6. This difference is statistically significant, but it is not very clinically important because the difference between 95.6% and 94.5% is only about 1%. Continuous pulse oximetry readings will frequently fluctuate by 2 to 4 percentage points on the same patient without any clinical changes occurring.

7. The oxygen saturation (like most biomedical measurements) is not normally distributed. Most biomedical measurements have a theoretical limit on their values. Oxygen saturation values cannot exceed 100%. Thus, if one creates a distribution of oxygen saturation measurements, it will show a few points below 80%, a few more points between 80% and 90%, a fair number of points between 90% and 95%, a large number of points between 95% and 100%, and no points about 100%. This is not bell shaped. Other examples of theoretical limits are: glucose values cannot go below zero, respiratory rates will not go below 10, etc.

8a. These groups are not significantly different. The mean plus or minus two standard deviations should contain approximately 95% of the area under the bell shaped curve. Thus, the shapes of these curves are wide with substantial overlap. It is not likely that these groups will be shown to be significantly different.

8b. These standard deviations are small, so the bell shaped curves are very narrow and they do not overlap each other. Thus, it is likely that these groups will be shown to be significantly different from each other.

8c. This one is not easily determined. A T-test would have to be run to calculate the p value. The two means are fairly close to each other, but the standard deviation is also small.

Chapter XXII.2. Evidence-Based Medicine
Claudine Kimura, MD

A 3 year old boy presents to the clinic with a cough for 2 days and a temperature of 99 degrees. He is noted to have a barking cough and other clinical findings consistent with a diagnostic impression of laryngotracheobronchitis or croup. After a discussion with the clinic attending, she mentions that dexamethasone may be a good treatment for this patient. You perform a literature search on PubMed and find an article entitled, "A prospective randomized double-blind study to evaluate the effect of dexamethasone in acute laryngotracheitis" (1).

One of the most exciting aspects of the practice of medicine is that it is continually evolving and changing. Every physician maintains the perpetual title of "Student of Medicine" as we are all constantly learning and absorbing new information. This, however, is also one of the most challenging and daunting aspects of the practice of medicine. Faced with thousands of articles every year, a practitioner can't help but feel overwhelmed at times. This is why the practice of evidence-based medicine is so important.

Evidence-based medicine (EBM) has been described as "a process of life-long, self-directed learning in which caring for our own patients creates the need for clinically important information about diagnosis, prognosis, [and] therapy" (2). It has also been described as "the process of systematically finding, appraising, and using contemporaneous research findings as the basis for clinical decisions" (3). The goals of evidence-based medicine are fourfold, and include: 1) improving the uniformity and standardization of care so that all patients receive optimal care; 2) helping providers make better use of limited resources by seeking the most effective treatments; 3) preventing harmful side effects or outcomes; and 4) making the literature accessible to all, thereby helping clinicians make the most informed decisions possible (3). Everyone, from the medical student to the most senior physician, can use the principles of evidence-based medicine. But, like any other worthwhile endeavor, it takes practice to become comfortable with and proficient in using these guidelines.

The basic tenets of evidence-based medicine are laid out in a series of articles published in JAMA, collectively entitled "Users' Guides to the Medical Literature" (4). There are over 25 different guides to EBM. The first two basic guidelines regarding articles on therapeutics (5, 6) and articles on diagnostic tests (7, 8) will be discussed here.

The basic process of evidence-based medicine involves seven steps (Table 1) (4). The first step occurs at the bedside, when a clinical question arises during the care of a patient. The question could be whether a test that was ordered will be likely to help make a diagnosis or if the present medication is the most efficacious for the patient's condition. The second step involves searching for sources of information. This might be as simple as asking a knowledgeable physician or looking in a textbook, but for the most comprehensive and up-to-date source of information, physicians turn to the medical literature. The simplest means of accessing the medical literature involves conducting a Medline or PubMed search using the internet. The third step is to identify the sources that are found, (i.e., identifying studies relating to the clinical question). The fourth step is to determine whether the results of the study being examined are valid. The specific guidelines for this will be outlined in the following paragraphs. The fifth step is to determine what the actual results are, for instance whether a test was able to accurately diagnose a particular condition. The sixth step is to determine whether the results are applicable to your patient, and thus helpful to you in caring for your patient. The last step is to the resolve the clinical question.

Table 1. Evidence-Based Medicine Approach to Clinical Problems
1. Identify the clinical question.
2. Search for sources of information.
3. Identify the source(s) found (relevant articles).
4. Determine whether the results are valid.
5. Determine what the results are.
6. Determine whether the results will help you in caring for your patients.
7. Resolve the clinical question.

The steps involved in evaluating an article on therapy are outlined in Table 2 (5,6). The first steps involve determining whether the results of the study are valid. Toward this end the article should first be scrutinized for randomization of patients. Many factors (e.g., age, sex, ethnicity, etc.), the least of which may be the therapy being studied, affect patient outcome. If the study population is large enough, randomization ensures that both known and unknown factors are evenly distributed between the treatment and control groups, making it more likely that any difference in outcome between the two groups is due to the treatment effect alone. In the croup article, the patients were randomized, as is noted in the title.

Table 2. Guide to an Article About Therapy
I. Are the results of the study valid?
  A. Primary guides
    1. Was the assignment of patients to treatments randomized?
    2. Were all patients who entered the trial properly accounted for and attributed at its conclusion? a) Was follow-up complete? b) Were patients analyzed in the groups to which they were randomized? ("intention-to-treat analysis).
  B. Secondary guides
    1. Were patients, health workers, and study personnel "blind" to treatment?
    2. Were the groups similar at the start of the trial?
    3. Aside from the experimental intervention, were the groups treated equally? Co-interventions (see below)?
II. What were the results?
  A. How large was the treatment effect? (see Table 3)
  B. How precise was the estimate of the treatment effect? (95% confidence interval)
III. Will the results help me in caring for my patient?
  A. Can the results be applied to my patient care?
  B. Were all clinically important outcomes considered?
  C. Are the likely treatment benefits worth the potential harms and costs?

Next, it is important to ensure that all patients enrolled in the study were properly accounted for at the end of the study. If there were a large number of patients "lost to follow-up," the results of the study may be skewed. To avoid having a therapy appear more effective than it is, assume that any "lost" patients from the treatment group had a "bad" outcome and those lost from the control group had a "good" outcome. It is also important to then evaluate whether the authors preserved randomization by using an "intention-to-treat analysis." This means that during the analysis of the study results, patients remain in the groups to which they were randomized in the beginning of the study, even if they are unable or unwilling to complete the treatment. If patients from the treatment group who were unable to complete the treatment because they got sicker are transferred to the placebo (control) group, the treatment may show more effect than is truly present, just because the placebo group has sicker patients. In the croup article, of the 29 patients randomized to the study, 28 were assessed at the 12 hour post-treatment mark, and 25 patients were assessed at the 24 hour mark. The reasons for the loss of the patients were given in the article. An intention-to-treat analysis appears to have been carried out by the simple design of the study, although this fact was not spelled out as such in the text of the article.

The next step is to determine whether patients and study personnel were "blinded" to treatment. It is well known that if a patient or worker knows that a patient is receiving the study medication, this will bias their assessment of the patient's outcome. It is then important to determine whether the two groups were similar at the start of the trial. If they were significantly different in any aspect other than the therapy (e.g., age, gender, ethnicity), this difference, and not the therapy, may account for any outcomes difference between the two groups. Next, it is important to ensure that both the treatment and control groups were treated equally in regards to any "co-interventions." Again, if one group received more of a co-intervention than the other, the outcome may be due to the co-intervention and not the therapy of interest. In the croup article, the patients and study personnel were both blinded. The groups did appear similar at the start of the study. In this study the rate of co-intervention use was one of the secondary outcomes measured, and the use of racemic epinephrine was found to be lower in the treatment group, but there was no difference between the two groups in rate of supplemental oxygen use.

The next set of steps involves evaluating the results of the study. This includes the computation of several formulas, listed in Table 3. Most trials evaluating therapy consider whether the therapy had a beneficial effect on some adverse outcome or event, such as hospitalization. One of the ways to express the difference in outcome is to calculate the absolute difference between the treatment and control groups: the absolute risk reduction (ARR). If "X" is the number (or percentage rate) of patients in the control group who were hospitalized, and "Y" is the number (or percentage rate) of patients in the treatment group who were hospitalized, then the ARR for hospitalization is "X-Y".

Table 3. Measurements of treatment effect
X = outcome in control group
Y = outcome in treatment group
Relative risk (RR) = Y/X
Relative risk reduction (RRR) = 1- Y/X
Absolute risk reduction (ARR) = X-Y
Number needed to treat (NNT) = 1/ARR

In the croup article, the primary endpoint was improvement in total croup score at 12-hour intervals after treatment. The severity of illness was measured using a "croup score," which was based on retractions, stridor, air entry, cyanosis, and level of consciousness. It was determined prior to the start of the study that an improvement in the total croup score of at least 2 points (out of a possible total of 17 points) would be clinically significant. At 12 hours after treatment, 13 of 16 patients (81%) in the treatment group had at least a 2 point improvement in their croup score, while only 4 of 12 patients (33%) in the placebo group had a similar improvement. A secondary endpoint was the need for racemic epinephrine aerosols, and whether there was a decreased need in the treatment versus the placebo group. In the placebo group 8/13 or 62% (X) of patients required an aerosol, while in the dexamethasone group 3/16 or 19% (Y) required similar co-intervention. The ARR for racemic epinephrine aerosol was (62%-19%) or 43% with respect to racemic epinephrine utilization as the comparison variable.

Another way to express the difference between the two groups is to calculate the relative risk (RR). The relative risk is the proportion of patients who experienced the adverse outcome in the treatment group as compared to the control group and is expressed as "Y/X". But the more common usage of RR is as the relative risk reduction (RRR). This is presented as a percentage and is calculated as [1-(Y/X)]. The larger the RRR, or the ARR, the more effective the treatment. However, it is important to understand the difference between the two values. If the results of a trial showed that 10 patients who received a placebo were hospitalized and only 5 patients who received a medication were hospitalized, the ARR would be (10-5) or 5. But the RRR would be [1-(5/10)], or 50%. A 50% reduction sounds better to most people than a reduction of 5, but in this scenario, the two results represent the same information. In the croup article, the RR for the requirement of racemic epinephrine aerosols would be calculated as 0.19/0.62, or 30%. The RRR would then be calculated as [1-0.30] or 70%.

The next step in evaluating the validity of a study's results is to determine how precise they are. This involves calculation of the confidence interval (CI). The CI is usually calculated as the "95% CI," which means that the true RRR lies within the range of the confidence interval 95% of the time. The CI speaks to the power of a study, and the factor which has the most impact on a study's power is its sample size. A study with 100 participants may have the same RRR as a study with 1000 participants, but the latter will invariably have a narrower CI and thus be more precise and the results more powerful. The 95% CI can be applied to absolute and relative values. Since a treatment would be deemed to be beneficial if the RRR (relative risk reduction) was greater than zero, the 95% CI would have to exclude zero in its range if the treatment is beneficial. For example, for a RRR study, a 95% CI of -0.1 to 0.4 cannot be statistically concluded to be beneficial since the value zero is contained within its confidence limits. However a 95% CI of 0.1 to 0.2, describes a statistically beneficial treatment, since zero is not included in the range (i.e., there is a less than a 5% chance that the treatment has no benefit).

The last set of steps involves determining whether the study you have just reviewed will help you to care for your patient. It is important to determine whether your patient is similar to the patients who were in the study you are investigating. If your patient would have met all the inclusion and exclusion criteria for the study, the results are likely applicable to your individual patient. It is also important to evaluate whether all significant outcomes were measured. The endpoint of decreased mortality as a result of treatment is always significant, but other outcomes, such as rate of hospitalization or subsequent morbidity, can also impact your patient's care. And lastly, the benefits and risks of the proposed treatment must be weighed for the individual patient. For the article on croup, you've decided that the results of the study are valid based on the study design, and you've evaluated the results of the study. You now determine that your patient is similar to those enrolled in the study, so the results can be applied to him. The study did not discuss any side effects or risks to the treatment, so the benefits of the treatment seem to outweigh the risks. You decide to treat your patient with a dose of dexamethasone.

The second set of guidelines entails the appraisal of articles on diagnostic tests. Table 4 outlines the steps involved (7,8). Again the first of these involves determining the validity of the study results. This includes evaluating whether there was a blind comparison of the test in question with a reference standard. This is important to determine how a new test measures up to the current "gold standard." Next it is important to determine whether the study included a sample of patients that is representative of the type of patients the test would be performed on in clinical practice. If the patients in the study differ from the type of patient who would require the test, the study may not be useful.

Table 4. Guide to an Article About a Diagnostic Test

I. Are the results of the study valid?
- A. Primary guides
  1. Was there an independent, blind comparison with a reference standard?
  2. Did the patient sample include an appropriate spectrum of patients to whom the diagnostic test will be applied in clinical practice?
- B. Secondary guides
  1. Did the results of the test being evaluated influence the decision to perform the reference standard?
  2. Were the methods for performing the test described in sufficient detail to permit replication?

II. What were the results?
- A. Are likelihood ratios for the test results presented or data necessary for their calculation provided? (see Table 5)

III. Will the results help me in caring for my patient?
- A. Will the reproducibility of the test result and its interpretation be satisfactory in my setting?
- B. Are the results applicable to my patient?
- C. Will the results change my management?
- D. Will patients be better off as a result of the test?

The next step is to ensure that all patients in the study underwent both the test in question and the reference standard. If only patients with abnormal results on the test being evaluated then underwent the reference standard, this would unfairly bias the results of the study, which is known as a "work-up bias." It is also vital to determine whether the methods used to perform the test were described with enough detail so that the results could be confirmed with a second study if necessary. If the test cannot be duplicated, it may be difficult to use in clinical practice.

The second set of steps involves evaluating the results of the study. The traditional method of defining the strength of a test is to determine its sensitivity and specificity. These are calculated using a "2x2 table" of the study results (Table 5). Sensitivity indicates the

probability that a patient with a particular disease (as defined by an established reference method*, commonly called a "gold standard") will have a positive test. Specificity indicates the probability that a patient without a disease will have a negative test (think of this as the true negative rate). The "2x2 table" can also be used to calculate positive and negative predictive values. Positive predictive value indicates the likelihood that a positive test will indicate the presence of a disease in a patient. Negative predictive value indicates the likelihood that a negative test will indicate the absence of a disease in a patient.

Table 5. Formulas for sensitivity, specificity, predictive value, likelihood ratios
For the given 2x2 table of results:

Test Result	Disease Present*	Disease Absent*
Positive	True Positive (a)	False Positive (b)
Negative	False Negative (c)	True Negative (d)

Sensitivity = a/(a+c)
Specificity = d/(b+d)
Positive predictive value (PPV) = a/(a+b)
Negative predictive value (NPV) = d/(c+d)
Positive likelihood ratio (+LR) = [a/(a+c)]/[b/(b+d)] = sensitivity/(1-specificity)
Negative likelihood ratio (-LR) = [c/(a+c)]/[d/(b+d)] = (1-sensitivity)/specificity

Another method of evaluating a diagnostic test is the likelihood ratio (LR). LRs indicate the accuracy with which the test in question confirms the diagnosis of a particular condition. The first step in using the LRs requires the determination of a pretest probability, which is the clinician's "gestalt" about the chances that a patient has a particular condition based on clinical information such as symptoms, risk factors, and physical examination. The LR then determines how a diagnostic test will affect the pretest probability, making a disease more or less likely, the outcome of which is called the posttest probability. This can be calculated using Bayes' theorem (rather difficult), but an easier way to determine the posttest probability by applying the LR is via a nomogram described by Fagan (9). Although this concept is a very useful and clinically important concept for clinicians, it is mathematically (even with the nomogram) difficult to determine. This concept is best understood with an example. If a patient with worsening right lower quadrant (RLQ) abdominal pain and classic symptoms/signs of appendicitis undergoes an ultrasound which is "negative for appendicitis", a clinician would be wise to ignore the ultrasound result and still suspect appendicitis as an etiology. If the clinical risk is low; however, such as in a fully ambulatory patient with minimal abdominal pain, appendicitis is very unlikely. Essentially, the diagnostic certainty is improved when the clinical impression is confirmed by the diagnostic test. In other words, if there is a high clinical probability and a positive test, then the patient most likely has that diagnosis. If there is a low clinical probability and a negative test, then the patient is not likely to have that diagnosis. If the clinical probability and the diagnostic test do not agree, then the diagnostic certainty is intermediate. In most situations, clinicians have an appreciation of these probabilities, but the numerical values can be difficult to measure. Bayes' theorem and Fagan's nomogram which are used to calculate a posttest probability, can be difficult concepts to grasp and cumbersome to use for those not familiar with them, but their advantage over the more widely used "sensitivity" and "specificity" are that they allow the clinician to apply the results from a research study to his or her individual patient.

An LR of 1 means the test offers no help is making the diagnosis since this means that the pretest and posttest probabilities are the same. The magnitude of the LRs affects their power to influence the posttest probability, i.e. the larger a positive LR the greater the likelihood the disease is present, and the smaller the negative LR the less likely a disease is present. See Table 6 for relative strengths of different LRs. LRs can be calculated via different means, including from the sensitivity and specificity of a test, as in Table 5. LRs are different from sensitivity and specificity because they take into account each individual patient, using the pretest and posttest probabilities.

The last set of steps again involves determining whether the results of the study will help you care for your individual patient. It is important to determine whether the test in question is feasible to perform and interpret in your setting. If a test requires special expertise to perform or interpret, the test may be less useful to you and your patient. It is also important to determine whether the results are applicable to your particular patient. If your patient has different co-morbidities or a different severity of disease, the results of the study may be less applicable, and the diagnostic test less useful.

It is also important to determine whether the results of the test will change your management. If you will not use the test to initiate treatment or determine prognosis, depending on the test's risk:benefit ratio, cost, and complexity, you may decide against performing it. Ultimately you must determine if performing the test will benefit the patient and whether the patient will be better off as a result.

Evidence-based medicine is a method for critically appraising and applying the medical literature. It is a tool, just like a stethoscope or history-taking skills, and can be immensely helpful in the day-to-day care of patients. No one can ever master all there is know in medicine, but the principles of evidence-based medicine can get you one step closer, one article at a time.

Table 6. Relative strength of Likelihood Ratios

LR >10 or <0.1	Large change from pretest to posttest probability.
LR 5 to 10 or 0.1 to 0.2	Moderate change from pretest to posttest probability.
LR 2 to 5 or 0.2 to 0.5	Small, but sometimes important, changes in probability.
LR 1 to 2 or 0.5 to 1	Small, rarely significant, changes in probability.
LR = 1	Pretest probability = posttest probability.

Questions

1. What are the 7 basic steps outlining the evidence-based medicine approach to clinical problems?
2. Why is randomization important?
3. What is an "intention-to-treat analysis?"
4. How do you calculate relative risk, relative risk reduction (RRR), absolute risk reduction (ARR), and number needed to treat (NNT), and what do these values mean?
5. What is the "95% confidence interval?"
6. Why is "blinding" important?

7. What are sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) and how do you calculate these values?
8. What are positive and negative likelihood ratios, and how do they differ from sensitivity and specificity?
9. How are pretest and posttest probabilities calculated and applied?
10. How can evidence-based medicine help you in your practice of medicine?

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9. www.pedsccm.org Pediatric Critical Care Medicine website with various resources and references for general evidence-based medicine.
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Answers to questions

1. I) Identify the clinical question. II) Search for sources of information. III) Identify the source(s) found. IV) Determine whether the results are valid. V) Determine what the results are. VI) Determine whether the results will help you in caring for your patients. VII) Resolve the clinical question.
2. Randomization ensures that both known and unknown factors are evenly distributed between the treatment and control groups, making it more likely that any difference in outcome between the two groups is due to the treatment effect alone.
3. This means that during the analysis of the study results, patients remain in the groups to which they were randomized in the beginning of the study, even if they are unable or unwilling to complete the treatment.
4. Relative risk reduction (RRR) = 1- Y/X. Absolute risk reduction (ARR) = X-Y. Number needed to treat (NNT) = 1/ARR. See Table 3.
5. The "95% CI," which means that the exact RRR lies within the range of the confidence interval 95% of the time. The CI speaks to the power of a study, and the factor that has the most impact on a study's power is its sample size.
6. It is well known that if a patient or worker knows that a patient is receiving the study medication, this will bias their assessment of the patient's outcome.
7. Sensitivity = a/(a+c). Specificity = d/(b+d). Positive predictive value (PPV) = a/(a+b). Negative predictive value (NPV) = d/(c+d). See Table 5.
8. LR for a positive test result (+LR) = [a/(a+c)]/[b/(b+d)] = sensitivity/(1-specificity). LR for a negative test result (-LR) = [c/(a+c)]/[d/(b+d)] = (1-sensitivity)/specificity. LRs are different from sensitivity and specificity because they take into account each individual patient, using the pretest and posttest probabilities.
9. The pretest probability is the clinician's "gestalt" about the chances that a patient has a particular condition based on clinical information such as symptoms, risk factors, and physical examination. The LR then determines how a diagnostic test will affect the pretest probability, making a disease more or less likely, the outcome of which is called the posttest probability.
10. a) Improves the uniformity and standardization of care so that all patients receive optimal care; b) Helps providers make better use of limited resources by seeking the most effective treatments; c) Prevents harmful side effects or outcomes; and d) Makes the literature accessible to all, thereby helping clinicians make the most informed decisions possible.

Chapter XXII.3. Epidemiology and Research Methodology
Loren Yamamoto, MD, MPH, MBA

You are seeing an obese 10 year old for a school physical. A history of his overall activity level indicates that he does not participate in sports, he stays indoors all the time and watches TV during the entire weekend. He doesn't know how to ride a bicycle. His only physical exercise is at school during recess and physical education classes. Because he is obese, the other kids make fun of him, so he prefers to just sit in the shade during recess.

His family history is significant for: 1) obesity in both parents; 2) cigarette smoking, coronary artery disease and hypertension in his father; 3) death from acute myocardial infarction in his paternal grandfather at age 45.

Exam: VS are normal except for his blood pressure which is 130/85. He height is at the 50th percentile. His weight is 84 kg (>95th percentile). He is very obese in no distress. His examination is normal except for the findings associated with obesity.

You advise his parents that he is at risk for heart disease in his early adult life if his obesity continues. You recommend a physical exercise program and suggest that his father should not smoke inside the home. However, his mother and father state that they are unable to comply because they live in an apartment. They don't believe that indoor exercises would help. They are skeptical and say that they would like to see some proof that exercise has some benefit. His father shows you a magazine article (from your waiting room) which states that cigarette smoking does not cause lung cancer.

You decide to look up some studies on the effect of exercise on obesity and cardiovascular disease. However, you find that there are many different types of studies and these are hard to compare and it is difficult to determine the quality of these studies. The statement about smoking is puzzling. The article states that although cigarette smoking is associated with lung cancer, it has not been shown to cause lung cancer. You decide to find out how experts determine if an association is truly due to cause and effect.

Epidemiology includes the description of methods which describe the occurrence of disease. Descriptive and inferential statistics are discussed in a separate chapter. Many epidemiology numbers are special descriptive statistics which help to summarize the occurrence of disease within a population. In clinical research, several types of studies exist. Understanding the differences between these study methods enables one to assess how good a study is in contributing to the clinical question at hand. This chapter will cover some basic epidemiology and focus on research methodology to develop an ability to critically appraise the medical literature.

Study design types (method of study) can be categorized into: 1) Experimental design, 2) Clinical trial (placebo controlled, blinded), 3) Cohort study, and 4) Case control study.

Recognizing what "type" of study one is reading is not nearly as important as recognizing the actual weakness of the data and its conclusions. Many studies do not fit neatly into one specific study type.

For the above 4 study types, they can be further classified as prospective, longitudinal, and retrospective based on the time sequence of the data observations. A prospective study generally looks at some time of exposure (a risk factor) and then determines at some future time, if a disease condition develops. Retrospective studies look at those who have developed a disease and then determine if any risk factors were present in the patients at some time in the past. Longitudinal studies make observations in the study group at several points in time moving forward.

Prospective and longitudinal studies are the most difficult to do because they require a long period of time to complete. Retrospective studies are easier to do, however, they are subject to numerous methodological flaws. Prospective and longitudinal studies are less subject to methodological flaws, so the quality of their conclusions is usually superior to that of a retrospective study.

1) The experimental design type of study is not common in clinical medicine using actual patients. This type of study is usually done in a lab using models or study subjects who are subjected to different treatments. It is nearly flawless from a methodological standpoint if it is done correctly. Example: Does 20-minute EMLA cream (a topical anesthetic) reduce the pain of starting an IV? Healthy study subject volunteers are recruited who are willing to have two IV's started on them. EMLA cream is applied to one hand and placebo cream is applied to the other hand with the study subject blindfolded. An IV is started on one hand and then the other hand. The study subject must now rank which hand was more painful. Note that this type of study could not be done on actual patients, because they would not ordinarily require two elective IVs.

2) The clinical trial is a study type that generally appears in the New England Journal of Medicine. Because such studies are very expensive to undertake, they have consumed enormous resources, and they have taken a long time to complete, it is unlikely that anyone else will have the resources to repeat it, and such studies are often fairly definitive in drawing conclusions. Clinical trials of new treatments must be compared to some type of control. The control could be an older treatment or it can be a placebo (placebo controlled). If patients know which treatment they are getting (the new treatment or the control), then the study is not blinded. This is a problem because patients may perceive they have gotten better if they got the new treatment and those who got the control (placebo or older treatment) may be less likely to feel like they have gotten better. The study design should somehow measure the patient's clinical response to treatment. It is best if this measurement is highly objective (e.g., blood sugar at 6:00 a.m.), but often it is a rather subjective measurement such as tympanic membrane abnormality or subjective pain relief. Even a measurement such as blood pressure may be subject to bias to some degree. If the measurement of clinical outcome has any degree of subjectivity, then it may be subject to bias if those making the measurements know whether the patient received the new treatment or the control. If those making the measurement are blinded as to whether the patient received the new treatment or the control, this removes the bias. This is blinding the study investigator. If possible, it is best to blind both the subjects (patients) and the study investigators (double blinded). Double blinding can be accomplished by assigning codes to pre-measured treatment vials. After the clinical outcome measurements are made, the code is revealed to determine which study subjects received the new treatment versus the control. It is not always possible to blind the patient or the investigator. For example, comparing the outcome a jogging program and weight control 2 years later, it would not be possible to blind the patient as to whether they were assigned to the jogging or non-jogging group.

3) In a cohort study, a group (cohort) is identified. Disease outcome and risk factors are assessed within the cohort. This can be done prospectively, longitudinally, or retrospectively. Examples:

Prospective: All patients in the emergency department (ED) arriving with wheezing are treated in an unrestricted fashion by the ED physician on duty. A data sheet is completed during the ED visit which indicates the patient's initial oxygen saturation, the number of bronchodilator treatments received, and whether the patient required hospitalization. This data can be analyzed to see if hospitalized patients have lower initial oxygen saturations compared to patients who were discharged home from the ED.

Longitudinal: The Hawaii Heart and Cancer Study, located at Kuakini Medical Center, enrolled all Japanese males of a certain age group on Oahu using selective service (military draft) registration data. Since the 1960s, this group of men has undergone periodic screening physical examinations, histories, lifestyle surveys, and laboratory studies. Since this cohort has been followed for a long period of time, many of the men have developed heart disease, cancer, etc. Such large longitudinal cohorts have yielded substantial information regarding the role of risk factors for such diseases. Other large cohorts are followed similarly in other research centers in the U.S.

Retrospective: 120 inpatient cases of intussusception were reviewed. Each chart was reviewed (retrospectively) to look for documentation of currant jelly stool and whether the diagnosis of intussusception was missed on the initial medical evaluation. The study concluded that the presence of frank currant jelly stool was associated with a low likelihood of missing the diagnosis of intussusception while there was a higher likelihood of missing the diagnosis in the absence of frank currant jelly stool.

4) A case-control type of study is always retrospective. Patients with a particular disease condition are identified (cases). A set of matched controls without the disease are found. Risk factors (exposure factors) are then compared in the two groups. For example, to examine the relationship of bicycle helmets on brain injuries, we could identify 30 patients hospitalized with brain injuries due to bicycle accidents. We could then go to a different hospital ward and find 30 patients of similar age and sex, but without a brain injury. We could then survey each group for the bicycle helmet use. If the bicycle helmet use frequency is 30% in the head injury group and 75% in the control group, and if $p<0.05$ for this difference, then an association exists to suggest that bicycle helmet use may lower the risk of bicycle related head injuries. However, there are other possible explanations for this so the strength of the conclusion is not as strong.

Clinical trials are the most difficult and expensive to do. Case-control studies are the easiest and least expensive to carry out. Cohort studies are in between. While case-control studies are the easiest to perform, they are the most subject to methodological flaws. In studying rare diseases, case-control studies are the most efficient means of epidemiological research. For example, in the Hanta virus epidemic in New Mexico, the most efficient way to determine risk factors for the deaths due to the unknown cause was to examine the background history of all the patients who died mysteriously compared to a group of matched controls.

Consider the example in the case in which we are trying to determine if lack of childhood exercise is associated with coronary artery disease (CAD) in later adult life. Using the four different study types, this is how it would have to be done:

For an experimental design, we would obtain 1000 young mice, since we could not do this study in humans. 500 mice would be exercised and the other 500 would be forced to be sedentary. When the mice become adults, we would look at their hearts to see how many in each group have CAD.

For a clinical trial, we would obtain 1000 child volunteers. We would then randomize them to childhood exercise or childhood non-exercise groups. Study volunteers would have no choice as to what group they would be in. Those assigned to the exercise group would have to exercise all through childhood. Those assigned to the non-exercise group would be forbidden from exercise throughout childhood. 40 years later as adults, we could survey them for CAD using angiography or a more sophisticated future method of imaging the coronaries. We would not be able to do a double blinded study since the study volunteers would know whether they were randomized to the exercise or non-exercise group. Such a clinical trial would be unethical and impossible.

In a cohort study, we would identify 1000 children who will be observed longitudinally for the next 50 years. There would be no restrictions on their lifestyle. Some will have a lot of exercise, some will have none and some will have intermediate levels of exercise. Somehow, this will have to be quantitated. Other factors associated with CAD must also be monitored, such as blood pressure, cholesterol, diet etc. In late adulthood, the cohort could be evaluated for CAD to determine whether more CAD is present in the groups who had less childhood exercise.

In a case control study, we would go to the coronary care unit (CCU) to find 50 patients hospitalized with ischemic cardiac disease. We would find 50 age and sex matched controls from the general hospital ward (without heart disease). We would then obtain a detailed history of their childhood exercise habits to see if there is less childhood exercise in the CCU patients compared to the controls.

In reviewing the medical literature, there are several common pitfalls in the interpretation of published data. Some of these include:

1. Gold standard.
2. Statistical significance versus clinical importance.
3. "Fishing" for a significant result: Data dredging.
4. Confounding variables.
5. Association versus cause & effect.
6. Case reports.

The gold standard refers to a method that truly identifies a particular condition. Some disease conditions have gold standards and others do not. Examine the following examples. Which of these are good gold standards and which of these are "bronze" standards?

Pregnancy: Positive beta-HCG, rising beta-HCG, baby/fetus/fetal tissue is eventually passed.

Meningitis: Elevated white cell count on CSF analysis.

Pneumonia: Characteristic CXR findings.

Appendicitis: Exploratory laparotomy examination of the appendix confirmed by histopathology.

In the above examples, the only one that is a poor standard (not "gold") is the CXR for pneumonia, since for a mild pneumonia, some radiologists would read the CXR as normal, while others would read it as a slight pneumonia.

Think of gold standards for the following examples that have been studied frequently in the literature: otitis media, strep pharyngitis, periorbital cellulitis, scaphoid fracture, bacteremia. The diagnostic standard for otitis media is, an examiner states that the patient has otitis media. This is a poor standard. The conclusions from many of the studies on otitis media are weak because it is not convincing that all the study subjects actually have otitis media. The diagnosis of strep pharyngitis is based on a throat swab. However, we know that some positive throat cultures are due to tonsillar colonization and not necessarily to strep pharyngitis. Periorbital cellulitis is a clinical diagnosis. Some would call a swollen bug bite on the upper eyelid a cellulitis. Scaphoid fractures are not always radiographically apparent. Bacteremia relies on a positive blood culture, but many blood cultures grow out contaminants and a negative blood culture may occur in bacteremia if the bacteremia is low grade. Thus, none of these diagnostic clinical entities are well defined by gold standards. If a gold standard is lacking, one cannot be certain what clinical entity is being studied.

Statistical significance versus clinical importance has been described in the chapter on statistics. Just because something is statistically significant does not necessarily mean that it is clinically important. For example small differences in white blood counts,

oxygen saturation values, pain scores may be statistically significant, but the differences need to be larger for them to be clinically important.

"Fishing" or "data dredging" for a significant result has been discussed in the statistics chapter. This phenomenon occurs when too many statistical tests are performed, which increases the likelihood that you will find a difference due to chance (which is not a true difference) leading you to an incorrect conclusion. Worded another way, the likelihood of a type 1 statistical error, increases with the number of statistical tests that are performed.

Confounding variables are variables that are related to the study risk factor and the outcome. Such factors must be matched or compensated for in order to compare two groups.

Example: Does watching Japanese language Samurai movies on TV cause GI cancer? We studied 50 men with GI cancer and found that 60% of them frequently watched Samurai movies. We then found a control group of teenagers from a high school who presumably do not have GI cancer. We found that 0% of the controls frequently watched Samurai movies. We thus, conclude that watching Samurai movies puts one at greater risk for GI cancer. What is wrong with this conclusion? Age is a confounding variable. Age is related to GI cancer since GI cancer tends to occur in older adults and not teenagers. Age is also related to the likelihood of watching Japanese language Samurai movies. While older Japanese men are somewhat likely to watch Japanese language Samurai movies, young teenagers are very unlikely to frequently watch these. Thus, to have a better control group, a confounding factor such as age must be matched for (i.e., the age distribution in the GI cancer group must be the same as that of the control group).

Age and sex are almost always confounding variables. Thus, comparison groups must always be matched for age and sex. Other confounding variables are more difficult to identify. Ethnicity is a significant confounding variable in the example above, since non-Japanese men are much less likely to watch Samurai movies.

See if you can think of some potential confounding factors for the following study. The emergency department carried out a study comparing special intraosseous needles with generic bone marrow needles to determine which needle was the easiest to use for an intraosseous (IO) procedure. Thirty Honolulu paramedics were asked to insert the special IO needle into a turkey bone, then to insert the generic bone marrow needle into a turkey bone. The two IO insertion times were recorded and the paramedics were asked to determine which needle they preferred. The following are the results. Mean insert time was 21 seconds for the special IO needle, and 15 seconds for the generic bone marrow needle, (p=0.02). 20% of the paramedics favored the special IO needle, while 80% favored the generic bone marrow needle (p=0.001). Identify some potential confounding variables?

1) These paramedics had previous experience and training with the intraosseous procedure. Which needle were they trained with and which needle have they used more in their experience? If they had previous significant experience with the generic bone marrow needle, then we would expect that they would have an easier time with this needle. Thus, previous intraosseous experience is potentially a confounding variable. This confounding variable could be corrected by matching those with previous generic bone marrow needle experience with others who have more special IO needle experience. Another way of eliminating this confounding variable is to use other study subjects, such as students, who have never performed an intraosseous insertion before.

2) Note that the study described above always started with the special IO needle, followed with the generic bone marrow needle. This gives the special IO needle a disadvantage because it gives the paramedics an opportunity to practice with a different needle prior to using the generic bone marrow needle, but no practice run is allowed prior to the special IO needle. If the turkey bone model is not similar to an actual intraosseous attempt, it may take some getting used to. The turkey femur is cylindrical, while an infant's tibia is flat. Thus, any practice on the unfamiliar cylindrical turkey femur may help to reduce the time of IO needle insertion. Thus, the sequence of which needle is used first is a confounding variable. This confounding variable could be eliminated by alternating or randomizing which needle is tried first.

How can we determine if the association between two variables is a mere association or if one causes the other? We often take this for granted. For example:

1. Measles virus exposure is associated with measles.
2. Asbestos exposure is associated with mesothelioma.
3. Stress is associated with shingles (zoster).
4. Cigarette smoking is associated with lung cancer.

Which of the above are mere associations and which are cause and effect? What objective criteria are you using to come to a decision?

Koch's Postulates are useful in determining cause and effect, but these postulates are applicable to infectious disease only:

1. The microorganism must be present in every case of the disease.
2. The organism can be cultured.
3. This cultured organism must cause the same disease when inoculated into another host.
4. The organism must be recovered and re-cultured from this new diseased host.

Although not as sound as Koch's postulates, the following criteria have been the standard for determining cause and effect. Epidemiologic cause and effect criteria include:

1. Strength and consistency of association (multiple studies show the same relationship).
2. Dose-response relationship (greater risk factor exposure results in greater risk of disease).
3. Correct temporal association (risk factor occurs first, then disease; not vice-versa).
4. Specificity of cause and effect (risk factor is specific for this disease; i.e., it does not cause other diseases).
5. Plausible reason for a cause and effect relationship to exist.

Are the following cause and effect under the above criteria?

1. Measles virus exposure is associated with measles. Yes.
2. Asbestos exposure is associated with mesothelioma. Very close to yes.
3. Stress is associated with shingles (zoster). No.
4. Cigarette smoking is associated with lung cancer. Probably, but not definite.

Stress does not meet the cause and effect criteria for zoster since the strength and consistency of the association is weak and the level of stress is difficult to measure, so a dose-response relationship is lacking. Stress and zoster are not specifically linked, since stress causes ill conditions other than zoster. Cigarette smoking does not meet cause and effect criteria because it does not meet the specificity criterion. Smoking is associated with GI cancer, lung cancer, esophageal cancer, oral cancer, heart disease, etc. If you have ever wondered why the tobacco industry claims that cigarette smoking is not a proven cause of lung cancer, this is the reason (lack of specificity). However, the reason for this is that cigarette smoke is not a homogenous substance and the pathogenesis of cancer is complex and multifactorial.

Single case reports should always be viewed with suspicion. Single case reports are only reported if the phenomenon reported is rare or unheard of. Such cases present a distorted view of reality. One could interpret case reports in the exact OPPOSITE way that they are presented. For example, if I wrote a "case report" about a child who got bit by a mosquito and then began to itch, no journal would ever publish this case report since we know that mosquito bites cause localized pruritus. But if I wrote a case report about a child who got bit by a mosquito and while scratching he invented a warp drive rocket engine, such an unexpected "case report" would be of interest to some journals. It has been said that you may choose to believe the exact opposite of a case report. In this case, getting bit by a mosquito does not cause one to invent an advanced means of interplanetary rocket propulsion. Additionally, if the case reported is so rare and it already occurred, it may not likely occur again.

Case series, on the other hand, are not subject to the same criticism as the single case report. Case series should be taken more seriously.

Screening tests: These terms are frequently misused.

Sensitivity=TP/(TP+FN)=the fraction of all true positives that are caught by the test. A very sensitive test identifies most of the true positives. However, there may still be a substantial number of false positives in a highly sensitive test.

Specificity=TN/(TN+FP)=the fraction of negatives that are true negatives. A very specific test correctly identifies most of the true negatives. However, there may still be a substantial number of false negatives in a highly specific test.

Positive predictive value=TP/(TP+FP)=the likelihood of having a disease if the test is positive.

Negative predictive value=TN/(TN+FN)=the likelihood of not having a disease if the test is negative.

Using tuberculosis (TB) as an example, primary screening tests should be very sensitive (catch most of the positives). TB skin testing is a useful primary screening test because it is positive in those with TB exposure (most of whom do not have pulmonary TB yet).

Secondary (confirmatory) screening tests should be specific. A negative CXR is likely to indicate the absence of pulmonary TB, thus, the positive skin test indicates TB exposure, but not pulmonary TB.

The negative predictive value is always high in rare conditions, regardless of how good or bad a test is. For example, is a serum beta-HCG a good test to rule out TB? Of course not. But did you know that its negative predictive value is 99% in ruling out TB. In a study sample only one in 200 TB skin tests was positive. All of these patients have negative B-HCG's. Thus, a negative B-HCG has a negative predictive value of 199/200=99.5% Wow!

Consider the following statement by Dr. Superstar: My clinical evaluation is 95% accurate in diagnosing appendicitis. What does this mean?

Does this mean that Dr. Superstar correctly identifies 95% of those with appendicitis (i.e., sensitivity=95%)? This may sound impressive at first glance, but I could roll a pair of dice and tell you that if I roll any number less than 13, the patient has appendicitis. Using this method, I will identify 100% of those with appendicitis. Of course there will be many false positives, but no false negatives. Rolling dice identifies 100% of those with appendicitis (i.e., sensitivity=100%).

Does Dr. Superstar mean that if he diagnoses appendicitis, then there is a 95% chance that the patient actually has appendicitis (i.e., positive predicative value=95%)? This may sound impressive at first glance, but consider the following: This could mean that Dr. Superstar evaluated 1000 patients. He made a clinical diagnosis of appendicitis in 100 patients, and of these 100 patients, 95 patients had appendicitis and 5 did not (positive predictive value=95%). Of the 900 patients who received a negative clinical evaluation by Dr. Superstar, 450 had appendicitis. Thus, Dr. Superstar could have a 95% positive predictive value, but this does not necessarily indicate that he is a good clinical diagnostician for appendicitis if he misses 450 cases of appendicitis for every 95 that he diagnoses.

Does Dr. Superstar mean that if he concludes that the patient does NOT have appendicitis, then there is a 95% chance that this is correct (i.e., negative predictive value=95%)? This may sound impressive at first glance, but remember the general statement made earlier about negative predictive value: The negative predictive value for any rare condition is always high regardless of how good or poor the test is. If Dr. Superstar evaluated 1000 patients and only 40 patients actually had appendicitis (4%), then I could use the dice test to predict which patients do not have appendicitis. Rolling any number less than 13 indicates the absence of appendicitis. This test will identify true negatives in 960 out of 1000 instances (i.e., negative predictive value=96%). Again, an obviously useless test, can often be better than a seemingly useful test. You must be careful in accepting some of these numbers.

There is a fallacy in the high percentages such as 95%. We tend to think that 95% and above for any kind of test is good, because all through our lives, we were taught that 95% was an "A grade". We needed these grades to get into college and medical school. The reality of these numbers is that 95% can be good, but it can also be very poor. THINKING is required to sort this out. Whenever sensitivity and specificity values are calculated, the author should ideally calculate all four values (sensitivity, specificity, PPV, NPV). If the author only publishes one or two of these, it is very likely that the unpublished values are very poor and do not support the author's conclusion. Such an omission should be viewed with extreme skepticism.

Special rate calculations are very common in epidemiology. These terms are frequently used incorrectly. Incidence is the number of new cases that occur. An incident rate is the incidence divided by some type of standardization factor such as a one year period (the annual incidence rate) or a clinical occurrence such as the total number of births as in the infant mortality rate (the number of infant deaths divided by the total number of live births). Prevalence is the number of cases that exist at a specific moment in time. A prevalence rate is the prevalence divided by some type of standardization factor (which cannot be a time period because by definition, prevalence refers to a single point in time and not a period of time) such as a population base. Because of these differences, incidence is generally used to describe acute conditions, while prevalence is used to describe chronic conditions. The incidence of a nursemaid's elbow might be 1000's

of cases per year. But the prevalence (how many have the condition now) of nursemaid's elbow at this very instant might be zero (or perhaps 1 or 2), because it is very likely that only 0, 1 or 2 children have this at this moment. The prevalence of childhood diabetes in a community might be 300 cases at this moment. If the number of new cases if childhood diabetes is about 35 per year, then we could say that the incidence of new onset diabetes (the initial onset is the acute event) is 35 per year. Thus, incidence underestimates the magnitude of the problem for chronic diseases since incidence only measures new cases.

Mortality rates are commonly cited to describe survival and the overall health of a community. Similarly, injury rates and other outcome rates can be used to describe the health of a community. Remember that the mortality rate for everyone is 100%. That is, all of us will eventually die. Therefore a mortality rate of 10% is impossible. This would make sense only for a time-limited mortality rate. Such as a 10-year mortality rate for leukemia is 11%. Which means that 10 years after the diagnosis of leukemia, there is a 89% chance of survival. All mortality rates should have a time period attached to them or it should be understood that the time period is short. The mortality rate for bacterial meningitis is 10%. Does this mean that if I have bacterial meningitis, I have a 90% chance of living forever? No, it implies that 10% of children with bacterial meningitis, die shortly after the diagnosis. It should be more accurately called a 1 year or 6 month mortality rate.

Mortality rates can be age adjusted which also permits the rate to be less than 100% because it is a calculated mortality rate corrected by the age distribution of the community's population. This calculation is beyond the scope of this chapter. Some examples of this will be described later. Infant mortality rates are frequently used to assess the health of a community or country. The implication is that a healthy community or country should have a low likelihood of an infant dying.

Consider the following CHALLENGING data interpretation examples:

Patients with angina who have coronary artery imaging studies often reveal the presence of coronary artery disease. Following coronary artery bypass grafting (CABG), patients' angina often resolves. What can be said about the observations in determining the utility of CABG? While these findings suggest that CABG reduces angina pain by improving coronary blood flow, a control group of "sham thoracotomy" patients (their chest was cut open, but no coronary grafts were performed) noted a similar degree of angina pain improvement following the "sham thoracotomy" procedure, suggesting that the thoracotomy itself had at least some role in reducing angina pain and this reduction in pain was not necessarily due to the coronary grafts. CABG recommendations were modified to recommend this procedure only in those with severe coronary disease.

Is phototherapy useful in the management of neonatal hyperbilirubinemia? Is bilirubin toxicity the cause of kernicterus? This is a complicated question, but in a study of ABO incompatibility patients with pre-set exchange transfusion criteria, babies were randomized to phototherapy or no phototherapy to see how many babies in each group reached the pre-set exchange transfusion criteria. There was no significant difference suggesting that phototherapy does not prevent the need for exchange transfusion in ABO incompatibility hyperbilirubinemia. Whether bilirubin is the cause of kernicterus is controversial and unlikely in my opinion since very high bilirubins are only associated with kernicterus if the cause of the hyperbilirubinemia is due to Rh incompatibility or G6PD deficiency. Other causes of high bilirubins are not associated with kernicterus. Bilirubin may be a marker of the actual cause of kernicterus, rather than be the cause of kernicterus itself.

In a study of 100 joggers compared with 100 age matched controls, the mean HDL was significantly lower than in the controls. What can be said about this data? It might be tempting to conclude that jogging improves HDL levels. However, joggers and non-joggers differ from each other in more ways than just jogging. It is likely that joggers have different diets than non-joggers. Multiple confounding factors exist such as diet, smoking, other exercise, work related stress, obesity, hypertension, diabetes, etc. All these factors are related to jogging and potentially to HDL. These confounding variables must be matched for among joggers and non-jogger controls.

Design a study to investigate whether IV magnesium prevents the need for intubation in severe status asthmaticus. When a severe asthmatic in near respiratory failure comes in to the ED, randomize the patient to magnesium or no magnesium and determine which group does better. This is not possible because, we would need to get consent from such patients to participate in such a study. It's not possible to get consent from such severely ill patients. All such patients get treated with multiple meds to prevent respiratory failure. Nothing should be held back. Any study claiming to have ethically randomized severe asthmatics, must not have been enrolling severe asthmatics; they must have enrolled moderately severe asthmatics who were stable for a consent procedure.

In a meta-analysis of ultrasound in the diagnosis of appendicitis, a scan of the literature identified 32 studies. 27 of these studies concluded that ultrasound is highly accurate in the diagnosis of appendicitis while 5 studies concluded that ultrasound is not accurate? The meta-analysis concludes that ultrasound is accurate. Comments? Several points here: 1) The more studies you see in the literature on a topic, the more controversial it must be. If the answer were clear-cut, no further publications on the topic are necessary. However, in controversial subject areas, multiple publications are often present in the literature, attempting to clarify the controversy. Thus, the correct conclusion should be that the accuracy of ultrasound in appendicitis is controversial. 2) There is publication bias towards studies with "positive" results. Thus, although 27 studies conclude positively that ultrasound is accurate and 5 studies conclude negatively, this doesn't mean that the positives outnumber the negatives, therefore the positive conclusion should not necessarily be reached. One negative study should have the weight of multiple positive studies since there is known publication bias favoring the publication of "positive" studies. 3) A study of ultrasound done by the University of XXX's Department of Pediatric Abdominal Ultrasonography Professors (i.e., superspecialists), should not be equated to the practice of general radiologists in community hospitals. A study conducted by superspecialists does not necessarily mean that a group of generalists can match the same results.

Consider the following statement: Trauma is the second leading cause of death. Gee, I didn't know that trauma was such a common cause of death. Trauma is the second leading cause of death only if the leading cause of death could be lumped into "non-trauma". There are ways to make any disease seem to be very important. For example, bicycle injures might be the first or second leading cause "accidental, non-motor vehicle related death in children 5 years of age". Additional phrases qualifying the death rate can be used to make any particular condition seem very important.

The U.S. has a higher infant mortality rate than Country-X (a very poorly developed country). How can this be? The U.S. defines a live birth as any birth with an Apgar score greater than zero. If a 21-week fetus (not compatible with survival) is passed with a heart beat of 10 beats per minute for 15 seconds until it stops, this is considered a live birth and an infant death in the U.S. Other countries do not count this as a birth. Thus, the U.S. infant mortality rate is not comparable to the way that infant mortality rates are measured in other countries. Very poor countries have poor health surveillance methods and probably don't know about most births and most infant deaths in their country, making their published infant mortality rates very inaccurate. Additionally, a very ill infant with complex surgical problems is transferred from another country to the U.S. where specialized surgical care is available. Despite heroic surgical efforts the infant dies.

This infant death is counted in U.S. statistics and not in the infant mortality rate of the country of the infant's birth. There are many things which distort the infant mortality rate making it an inaccurate proxy for the health status of the U.S.

A study is done to determine the most common causes of pneumonia in young adults presenting to a college student health clinic. Blood cultures are drawn from the first 500 patients diagnosed with pneumonia. Of these 500 blood cultures, 15 grow pneumococcus and 4 grow staph epidermidis. The study concludes that only 0.2% (15 out of 500) cases of pneumonia are due to pneumococcus. Comment on this conclusion. A blood culture is a not a gold standard for determining the cause of the pneumonia. Many patients with pneumococcal pneumonia have negative blood cultures. Staph epidermidis is often a contaminant and is very rarely a cause of pneumonia. Other causes of pneumonia such as mycoplasma and viruses will not be recovered from a blood culture.

A study was done to determine if a single IM dose of ceftriaxone (Rocephin) was sufficient to cure otitis media. This study randomized children with OM to receive 10 days of amoxicillin or a single IM dose of ceftriaxone. After 10 days, roughly 67% of children were found to be cured in both groups. The study concludes that single dose ceftriaxone is effective in treating otitis media. What are the problems with this study? In a study comparing amoxicillin with placebo in the treatment of otitis media, cure rates were roughly the same in both groups. Thus, ceftriaxone is similar to placebo in efficacy or similar to amoxicillin in efficacy. If similar to placebo, then one would conclude that ceftriaxone doesn't work, but if similar to amoxicillin, one would conclude that it does work. Unfortunately, we can conclude neither because the definition of OM is poor (no gold standard). It is likely that most cases of OM are minor and don't require treatment, so if the study deliberately enrolled patients with minor OM, then the spontaneous cure rate would make it appear that both groups got better at the same rates. Drug companies might deliberately set up a study to have a favorable conclusion. Notice that they chose to compare ceftriaxone to amoxicillin rather than to placebo because if the cure rates were shown to be similar to amoxicillin, the conclusion would be that ceftriaxone is effective, but if the cure rates were similar to placebo, then the conclusion would be that ceftriaxone is ineffective. When you do a study consisting of 980 cases of minor OM and 20 cases of severe OM, any treatment benefits will be diluted by the 980 minor cases that don't benefit from treatment. The problem here is that there is no gold standard to define the disease condition being studied and the heterogeneity (minor cases mixed with severe cases) of the condition being studied.

Questions

1. At the Acme emergency department, the hospitalization rate for all ED patients is 6%. The emergency physicians at Acme have developed a test to predict the need for hospitalization. When this test is positive, there is a 93% chance that the patient will NOT need hospitalization. Is this a useful test?

2. In a meta-analysis of midazolam (Versed) sedation in children undergoing procedures, a scan of the literature identified 10 studies. 7 of these studies concluded that midazolam was highly efficacious in accomplishing sedation without significant adverse effects. Three studies concluded otherwise. The meta-analysis concludes that midazolam is an effective agent for pediatric sedation. Comments?

3. True/False: Sweden and Norway have lower mortality rates than the U.S.

4. Poor country PP has a border with a wealthy country WW. The age adjusted mortality rate for WW is higher than for PP, suggesting that PP is a healthier country than WW. This is obviously not the case as one can observe by traveling through both countries. How can this discrepancy be explained?

5. You read in a textbook of medicine citing the incidence and prevalence of diabetes mellitus. Which number (incidence or prevalence) is more useful to describe the epidemiology of diabetes? When is one preferred over the other? How accurate are these numbers? Where do these numbers come from?

6. Define sensitivity, specificity, positive predictive value and negative predictive value. Which of these is frequently >90% even if the test is a poor one?

7. Is it possible to have a test that has a nearly 100% sensitivity, specificity, positive predictive value and negative predictive value? If so, give an example of such a test in clinical medicine.

References:

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2. Kramer S (ed). Mausner and Bahn Epidemiology: An Introductory Text, 2nd edition. 1985, Philadelphia: W.B. Saunders Co.

Answers to questions

1. No. Since the Acme emergency department has a hospitalization rate 6%, we know that 94% are not hospitalized. By just stating that all patients do not require hospitalization, I have a 94% chance of predicting this correctly. Therefore, no test at all is better than the 93% predictive value of the Acme physicians' tests. Although 93% sounds like a good number, it is actually a poor number in this case.
2. The more studies you see in the literature on a topic, the more controversial it must be. If the answer were clear-cut, no further publications on the topic are necessary. However, in controversial subject areas, multiple publications are often present in the literature, attempting to clarify the controversy. Thus, the correct conclusion should be that the efficacy of midazolam for pediatric sedation is controversial.
3. No matter what country you live in, we all eventually die. The mortality rate in all countries is 100%.
4. It could be that since PP is so poor, they don't have an organized health department which keeps accurate health statistics. When the World Health Organizations asks PP to submit their age adjusted mortality rate, the health minister in PP just writes down any number and sends it in. This random number just happens to be lower than the accurately determined age adjusted mortality rate submitted by WW. Another explanation is that since PP has such a poor health care system, any patient who is very ill, is illegally smuggled over the border into WW where the patient shows up in an emergency room. The ethical staff in WW hospitals take care of these very ill patients who frequently die. These death statistics are registered in the health statistics of WW. Thus, many deaths that should have been attributed to PP, actually show up in the age adjusted mortality rate of WW instead. Such a phenomenon could make it appear that many people in PP never die.

5. Prevalence is better for diabetes. Chronic diseases are best described with prevalence while acute diseases are best described with incidence. These numbers may not be very accurate. They may come from disease condition registries or from health department statistics. These systems require that hospitals and/or physicians send in report cards diagnosing the patient's condition so that the statistic can be kept. However, such reports are frequently not made even in "reportable" diseases which the law requires to be reported. Diabetes is not a reportable illness. Another source may be health insurance claims information which contain diagnostic codes.

6. Sensitivity=TP/(TP+FN)=the fraction of all true positives that are caught by the test. A very sensitive test identifies most of the true positives. However, there may still be a substantial number of false positives in a highly sensitive test. Specificity=TN/(TN+FP)=the fraction of negatives that are true negatives. A very specific test correctly identifies most of the true negatives. However, there may still be a substantial number of false negatives in a highly specific test. PPV=TP/(TP+FP)=the likelihood of having a disease if the test is positive. NPV=TN/(TN+FN)=the likelihood of not having a disease if the test is negative. The NPV frequently has a deceptively high value, such as >90% if the disease condition is infrequent.

7. It is possible. Most of these tests are gold standards since they are nearly perfect and they actually define the disease entity. But generally if a study publishes only two out of these four values, it is likely that are publishing the two best values and the authors have suppressed the other two values which do not appear as good. A test which is has nearly perfect sensitivity, specificity, PPV and NPV is the pregnancy test. Lumbar puncture for meningitis is also quite good. Radiographic images for certain types of fractures which are obvious (e.g., forearm fractures) are also quite good.

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